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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 19 1953

ALMROTH WRIGHT—PIONEER IN IMMUNOLOGY*

BY

LEONARD COLEBROOK, F.R.C.S., F.R.C.O.G., F.R.S.

Almroth Wright was not much given to boasting, but, like Bernard Shaw, he sometimes took pleasure in shocking people by a remark that smacked of arrogance. On one such occasion, when a visitor to his laboratory, who had been rather talking down to him, asked whether he had read a certain paper, Wright replied somewhat tersely, "No, we don't read bacteriology—we make it."

The time has come, I think, when we may profitably consider how far he did "make bacteriology," and perhaps ask ourselves whether some of the unconventional ideas he stood for may not be worthy of re-examination.

When he graduated in 1883 (from Trinity College, Dublin) medical bacteriology was beginning to make quite a stir in the world. The great mystery of tuberculous disease (which was killing 1,000 people a week in England and Wales) looked a little nearer a solution with Koch's discovery of the tubercle bacillus in 1882. A year before that he had shown that many microbes could be grown, and pure cultures obtained, on solid nutrient media. A year later he isolated the cholera vibrio. In France, too, great things were happening. The patient work of Davaine and Pasteur and others had at last established the relationship of *Bacillus anthracis* to anthrax; and by his classical experiment with 50 sheep Pasteur had shown that it was possible to make animals immune to that deadly disease by the inoculation of an attenuated culture of the bacillus.

Very soon the concept of "antibodies" was born—from the work of Ehrlich and von Behring, of Roux, and of Pfeiffer. Antitoxins were detected in the blood of animals inoculated with the poisonous principles contained in cultures of diphtheria and tetanus bacilli. A little later a bactericidal antibody was discovered in the peritoneal fluid of guinea-pigs which had been inoculated with a killed culture of the cholera vibrio. And after that yet another antibody (agglutinin) was found which caused the clumping of typhoid bacilli by the serum of animals inoculated with that microbe or of man suffering from typhoid fever.

Diagnosis and Prevention of Typhoid Fever

It was at this point that Wright started his bacteriological work—in 1893. He had recently been appointed Professor of Pathology in the Army Medical Services, with his headquarters at the Royal Victoria Hospital at Netley on Southampton Water. There he frequently saw men suffering from typhoid fever, and others invalided home with Malta fever, and some with fevers to which it was not easy to attach a diagnostic label. There was no such thing as laboratory diagnosis in those days—nor, indeed, in most hospitals was there any laboratory. But the clumping of typhoid bacilli by serum quickly suggested to Wright, as well as to others on the Continent, that it might be possible to develop a laboratory test which would serve for the differential diagnosis of typhoid from "Malta" and, perhaps, other fevers.

In devising a technique for carrying out such a test Wright made his first contribution to bacteriological methods—the use of a wide-bore, graduated capillary pipette instead of the more conventional test-tube. As an indirect result of this work Wright was soon able to demonstrate that Malta fever was not by any means confined to that island.

Then he turned his attention to the *control* of typhoid fever, which was a serious public health problem in those days. In England it was killing 5,000 people a year, and in the U.S.A. 15,000. The British Army serving abroad lost many men from it even in peacetime, and had far heavier losses in every campaign. Ten years had gone by since Pasteur's great achievement with immunization against anthrax, and no one had attempted a similar preventive therapy in man by the inoculation of a bacterial vaccine. But things were moving in that direction. Haffkine, a Russian bacteriologist who had been working at the Pasteur Institute, was making plans to carry out anti-cholera inoculations in India. On his way there he visited Wright at Netley, and in course of conversation suggested that it might be worth trying a similar procedure against typhoid.

Wright promptly took up the idea. It had been shown in Germany that the destruction of cholera vibrios in the peritoneum of a guinea-pig was brought about by the agency of a bactericidal antibody in the animal's circulating blood. Wright saw that, if it was possible by an inoculation of vaccine to elicit the formation of a similar bactericidal antibody to the typhoid bacillus in the circulating blood of a man, it would probably constitute a barrier against the invasion of his blood stream by those bacilli from the intestine. It might even prevent the intestinal infection itself.

He went to work on that concept—but there were difficulties. Pasteur had used an attenuated but still living culture for the inoculation of his animals; and had demonstrated their immunity by "challenging" them with a dose of virulent culture which would certainly

*Being the first of the 1953 series of Almroth Wright Lectures delivered at St. Mary's Hospital on June 5.

kill an uninoculated animal. Wright "saw with his mind" that it should be possible to employ a non-living vaccine (this had indeed been done with the cholera guinea-pigs in Germany), and that it should also be possible to get evidence of a man's response to the inoculation by testing his blood *in vitro* for bactericidal antibody. But no test of that kind was then known. So Wright devised one, using, as he always did, very simple tools—a little glass tubing, a blow-pipe, some rubber teats, and a glass-writing pencil. The procedure he achieved remains to this day a model of ingenuity, and has not been improved upon for the object Wright had in view. It enabled him to determine approximately how many typhoid bacilli would be killed by a given volume of serum.

Then he began his inoculations—on himself and some of the "surgeons on probation" working in his class at Netley. Very soon his tests of the blood showed that, following the inoculations, there was usually a big increase in its power to kill typhoid bacilli—often a hundredfold or even more—and this enhanced power was maintained for weeks or months.

To Wright that meant that it would probably be possible to protect soldiers against typhoid fever. Preliminary trials on volunteers in the Indian Army gave encouraging results, but when Wright urged the War Office to mount a large-scale trial on troops embarking for the South African War there was immediate opposition. Some of those in authority were not at all impressed by what happened in Wright's capillary pipettes; they wanted clear-cut statistical proof that the men would in fact be protected by the inoculations. Such proof could, of course, not be obtained until a large-scale trial had been made.

So it happened that less than 4% (about 12,000 men) of the troops were inoculated, and during the three years of that war the Army had nearly 58,000 cases of typhoid, with about 9,000 deaths. Although an attempt was made to collect evidence of the degree of protection afforded to the inoculated men the conditions of active service made it very difficult to get reliable data. Dr. John Freeman has told how, when he visited a hospital where there were some cases of typhoid, he asked the sergeant in charge whether they had been inoculated. The reply was, "Oh, yes, Sir; I always scores 'em up as inoculated, because it stands to reason that they wouldn't have got typhoid if they hadn't been."

Statistical Data

After the war Wright might well have let the matter rest. He had published his laboratory data about the increased bactericidal power, and he could have left it at that. Most men would have done so. But his experience with the War Office had made him realize that the proposal to inject microbes, whether dead or alive, into healthy human beings was bound to arouse antagonism—it was too novel. And Wright was not half an Irishman for nothing. So after the war he continued to press for proper statistical trials to be carried out by the Army, with the result that ultimately, in 1909, satisfactory data were produced by his successor at Netley, Colonel W. B. Leishman. Table I shows that the records, obtained with special precautions against error, were strongly in favour of the use of vaccine.

TABLE I.—*Antityphoid Inoculation in Sixteen Units of the British Army Serving Abroad During 1905–9*

	No.	No. of Cases of Typhoid Fever	No. of Deaths from Typhoid Fever
Inoculated	5,473	21	2 (i.e., 0·38 per 1,000 inoculated men)
Uninoculated ..	6,610	187	26 (i.e., 3·93 per 1,000 uninoculated men)

Table taken from Leishman, *J. roy. Army med. Cps*, 1909, **12**, 163.

A little later a similar trial, with similar results, was reported by Colonel Russell, who compared the data from two camps in the U.S., one of which had all the men inoculated and the other very few. The records are shown in Table II.

TABLE II.—*Typhoid Fever in Two Comparable Camps of the United States Army (Both with a Good Water Supply)*

	Uninoculated	Inoculated	Cases of Typhoid	Deaths
Camp A (1909)	82,100	1,900	282	22
„ B (1913)	0	91,000	3	0

Figures taken from Russell, *War Dept. Bull. Wash.*, No. 2, 1914.

Had it not been for the striking success of these trials between the wars we might well have entered upon the first world war with our fighting Forces uninoculated. As it was, an active policy of immunization was adopted from the beginning in all Services, and by the end of 1915 almost 100% of our Expeditionary Force had been inoculated. As the war went on cultures of paratyphoid A and B were added to the vaccine.

The sickness and deaths due to enteric fevers in that war are shown in Table III and compared with the figures for the South African War.

TABLE III

	Annual Incidence per 1,000 Strength	Annual Death Rate per 1,000 Strength	Total Cases	Total Deaths	Mean Strength
South African War, 1899–1902 ..	105·00	14·6	57,684	9,022	208,226
1914–18 war ..	2·35	0·139	20,139	1,191	2,000,000 (approx.)

Table taken from the *Medical and Surgical History of the Great War* (Section of Pathology, p. 211). 1923.

It has been estimated that if our losses from typhoid and paratyphoid fevers during the first world war had been on the same scale as in South Africa there would have been nearly 1,000,000 cases and about 125,000 deaths. They might easily have been on a greater scale, since the land fighting in the 1914–18 war was chiefly trench warfare and fought along the Franco-German frontier, where typhoid was always endemic. Not all the reduction of incidence and mortality from enteric fevers in the first world war can be ascribed to the policy of inoculation, because in the years between the wars there had been progress also in military hygiene—particularly with regard to water supplies—but in view of the figures shown in Tables I and II it seems very probable that a large part of the improvement was the result of immunization.

That great achievement—the control of typhoid fever—will always stand out as one of the biggest landmarks of medicine in the twentieth century. History will surely award the credit for it, in the first place to Pasteur for his pioneer work on anthrax in animals, and after him to Wright. Wright had certainly "made" bacteriology—by his masterly elaboration of a method of measuring the antibody response in the inoculated man, so affording a guide to that procedure; by his method of enumerating the bacterial bodies in his vaccine, and so making dosage more precise; and by his dogged fight to get the vaccine used in the British Army against considerable opposition.

Vaccine Therapy

When that work was done Wright left the Army Medical Services (1902) and came to St. Mary's as Professor of Pathology and Bacteriology. Speaking of that appointment in later years, he used to say that every large hospital needs two staffs—one to teach all that is known, the other to teach that we don't know anything, and to get on with it. "Getting on with it" meant for Wright embarking upon a fresh chapter in the story of immunization.

In this undertaking Pasteur was again his leader, for Pasteur had shown that it was possible to do preventive inoculation successfully in the case of rabies even when the patient had been bitten by a mad dog *several days before* the inoculations were given. Reflecting upon this, Wright said to himself: "The microbes introduced by the bite have only won a bridgehead—the rest of the man's tissues are uninfected and should be able to respond to an inoculation just as the tissues of a healthy man against typhoid." And he went on to apply the same conception to other localized infections. At Netley he had seen a number of men suffering from boils. "Were they not," he asked himself, "in much the same case as the man bitten by a mad dog?"

As he pondered upon this another question arose in his mind. "How does the man with a boil recover from his infection?" Tests of the blood of men with boils had shown that there was no bactericidal antibody to the staphylococcus. There must then be some other mechanism. Metchnikoff's recent work suggested that it might be phagocytosis, and Wright decided to go to work on that hypothesis. But very little was known about phagocytosis—and there were no methods for studying it. Gradually a plan took shape in Wright's mind. He must first devise methods for finding out whether the blood of a sick man had less capacity for phagocytosis than that of a healthy man; and, if it was so, whether it was possible to increase his phagocytic activity by appropriate doses of vaccine—in other words, "to build up his resistance."

That was an entirely new approach to infectious disease—and it called for a lot of preliminary work in the laboratory. Very soon this brought an unexpected discovery. When he collected leucocytes from his own blood and washed them free of serum (by the centrifuge), and then mixed them up with microbes, there was almost no phagocytosis, but when serum was present in the mixture it was abundant. Apparently there was something in the serum which made the microbes acceptable to the leucocytes. Wright christened it an "opsonic factor" from the Greek word *opsono*=I prepare victuals for.

That discovery immediately suggested to Wright that he might *measure* this opsonic factor in the serum of different individuals, and in the serum of the same individual before and after an inoculation of vaccine. To do that he had first to prepare the way by a series of technical tricks. He had to devise a convenient method of collecting small samples of blood (for the syringe in those days was a rather primitive affair). For this he again resorted to glass tubing—and "Wright's capsule" gradually evolved. Next he had to find a method of spreading blood films in such a way that the leucocytes were all assembled at one end, more or less in a straight line, like soldiers on parade. This he achieved by means of the "spreader"—a microscope slide broken across in such a way that the line of fracture presented a very slightly concave arch. When a drop of blood was drawn along under this arch the leucocytes, being larger than the red cells, were carried to the end of the film. Thirdly, he had to find out how to prepare a suspension of leucocytes from blood in such a way that they would retain their capacity for phagocytosis for some hours.

"Therapeutic Immunization"

When these preliminaries were completed Wright was ready to embark upon his plan of "therapeutic immunization." Very soon the laboratory off the museum became a sort of unofficial out-patient department where, at almost any hour of the day, you might have found patients waiting to have a sample of blood taken or to get an inoculation. And at almost any hour of the night you might have found Wright and his assistants—Douglas, John Freeman, Alexander Fleming, and others—patiently working out the "opsonic indices" of those specimens of blood; or discussing, over that midnight cup of tea, the progress of this or that patient. And frequently there were visitors from other countries helping with the work, for this new concept of Wright's had kindled the imagination of doctors all over the world. St. Mary's was, for the time being, the centre of the medical stage.

It would not be very profitable to-day to discuss in any detail that campaign of vaccine therapy. We tried it for all kinds of infections: for boils and carbuncles, for erysipelas, for tuberculous glands and joints and lupus, for phthisis, for urinary and respiratory tract infections. No attempt was made to assess the results by statistical methods, partly because the clinical material was much too heterogeneous to give data of any value, and partly because Wright himself held strong views about the fallibility and the pitfalls of statistical procedures applied to medical problems.

There were some striking successes, and quite a few failures (especially in septicaemic conditions and phthisis), and in many other cases it was difficult to be sure how much the patient's recovery had been assisted by our treatment.

Looking back, it seems to me that the road Wright took was well worth while at that time, when neither the sulphonamides nor the antibiotics were on the horizon. We certainly learned much about infections and the response to inoculations of vaccine; and we helped many people. I think we might have won more substantial scientific gains if we had concentrated our attack upon a smaller target, treating fewer patients; and perhaps studying the effect of vaccines in some animal infections so that we could have checked our clinical impressions by experimental investigations and by statistical comparisons. To-day, after nearly 50 years, we still have little precise knowledge about the train of events set going by an infection or an inoculation of vaccine. Wright's working hypothesis that phagocytosis, activated by an opsonic antibody, was the dominant factor may well prove to have been too simple. He himself, in his later years, abandoned the view that opsonic power of the serum *per se* could serve as an indication of a patient's resistance; but he held to the belief that the key to that resistance must be sought for in the circulating blood. And he spent 20 years in that search. It may be that, with fuller understanding of the factors which make for recovery from a microbic infection, future years may see a return to Wright's programme of evoking the body's potential response to an immunizing stimulus.

Summarizing, I think one may fairly say that in this phase of his life Wright did again "make bacteriology" by his discovery of the opsonic power of serum, which "married" the concept of salvation by phagocytosis with that of humoral antibodies; by his many technical devices for the study of phagocytosis; by working out some of the principles of therapeutic immunization; and, perhaps not least, by bringing the whole medical profession to think of infectious disease in terms of microbes and the patient's resistance to those microbes. Together these constituted a notable advance in the application of science to medicine, and in that advance Wright was unquestionably the leader.

Infections of War Wounds

During the first world war Wright did perhaps his best scientific work. That war quickly brought many new problems. High explosives were being used on a scale never known before and were causing terrible injuries which gave rise to appalling sepsis. Gas-gangrene became a frequent instead of a rare event. For the first time in the history of war medical research was called upon to play its part. Wright, with Fleming, was commissioned to set up a laboratory in France for the study of these wound infections.

The surgeons of that day had just witnessed the astonishing disappearance of sepsis in their civilian work, following the application of Lister's principles and asepsis in the operating theatres. From that experience there had grown up a largely uncritical faith in the ability of all sorts of antiseptic substances to cope with the bacterial infections of wounds, and it was assumed that these same agents would suffice in war emergency. But that hope was quickly disappointed—the antiseptics appeared to have little or no effect. Great numbers of men were dying or losing their limbs, sometimes even when their injuries were comparatively slight.

Wright, almost alone, saw what was happening. Although the antiseptics killed microbes so well in test-tubes they were not killing them—or even restraining their growth—in the wounds. Reflecting upon this, he recalled the earlier work of Koch and von Behring, which had shown that, whereas perchloride of mercury in watery solution would kill anthrax bacilli at a dilution of 1 in 1,000,000, the solution required to be 100 times as strong if the antiseptic was dissolved in serum. And Wright had found the same thing with some other antiseptics. Apparently they forfeited much of their antiseptic potency by combination with serum proteins. As Wright put it, they were "quenched."

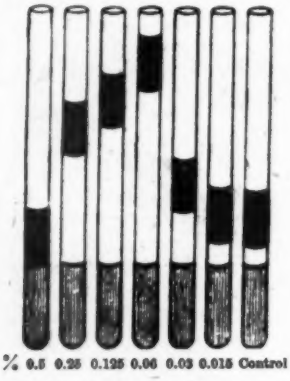

FIG. 1.—Antiseptics can favour the growth of microbes in blood (Fleming).

The situation was even worse than that, for on investigation it transpired that many antiseptics, when added to serum in concentrations which failed to kill microbes, actually *favoured their growth*. This effect was well shown by Fleming in the experiment illustrated in Fig. 1. Here several volumes of serum, equally inoculated with a gas-forming anaerobic bacillus, received increasing amounts of carbolic acid (from right to left), and were then covered with sterile melted petroleum jelly. (The volume of gas formed under the plug of petroleum jelly served as a rough indicator of the amount of growth in the serum.) It is seen that, whereas there was little gas-formation in the control serum, it increased very considerably with each addition of carbolic from a concentration of 0.03 to 0.06%, and was suppressed only when the concentration reached 0.5%—a strength at which blood cells and most fixed tissue cells would be severely damaged or destroyed. There can be little doubt that the application of dilute solutions of antiseptics to wounds in the past must often have resulted in an *increased* growth of microbes, as shown in this experiment, rather than in a suppression of growth.

There was a second reason why the antiseptics so often failed to check microbic growth. They did not reach the microbes, which were hidden in a thousand nooks and crannies among torn muscle fibres, impacted bony fragments, etc. Another experiment of Fleming's illustrated this difficulty in a striking fashion. The lower end of a test-tube was pulled out into spikes as shown in Fig. 2 to simulate a ragged wound cavity. It was then half-filled with serum broth and heavily inoculated with a great variety of microbes from an infected wound, and incubated. Next day, when there was a profuse growth, it was emptied out and the tube refilled with a strong antiseptic solution, which was left for some hours. This in turn was thrown out and the tube again filled with *sterile* broth and incubated—to see whether any microbes had remained alive. The result was always the same. Whatever antiseptic had been used the broth yielded a copious growth. Evidently the antiseptic had failed to reach the microbes in the tips of the spikes.

Having satisfied himself that there was little or nothing to be hoped for from the antiseptic policy, Wright decided to go back to the beginning and try to find out what was happening in the wounds. First he must know what were the conditions which allowed so great a swarming of microbes in them. Would the fresh lymph as it exuded into a wound support such a copious growth of many species? or did this occur only in exudate after it had lain in the wound for a time and become changed? To answer that Wright collected small samples of fresh lymph in what he called a "lymph leech"—a simple contrivance for exerting gentle suction on the wound wall. When he incubated lymph collected in such a "leech" he obtained only a sparse growth of microbes, and usually only one or two species—streptococci or staphylococci; whereas fluid which had been incubated by the patient himself in his wound cavity showed some 20 to 30 species growing in great profusion. It appeared, therefore, that certain microbes were able to multiply to some extent in fresh lymph while others would grow freely only in stale exudate.

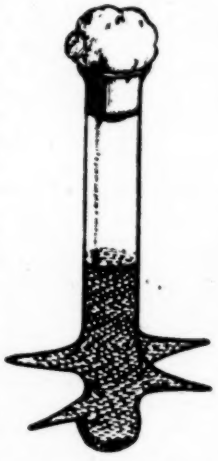

FIG. 2.—Fleming's experiment on the failure of antiseptics to sterilize wounds.

Wright next asked himself: Were there nutrient substances available in the stale lymph which were not present in the fresh? Reflecting upon this, he recalled two recent discoveries which might well throw a light on these findings. Opie, in New York, had found that the pus of tuberculous abscesses contained proteolytic ferments which he believed were set free from the disintegrating leucocytes. And other American workers, Jobling and Peterson, had demonstrated that normal human serum exerted an *antiproteolytic* effect. In the wounds there were plenty of distintegrating leucocytes, and if proteolytic ferments were being produced from these they would probably break down the proteins of the exuding lymph to provide simpler foodstuffs for microbic growth. These proteolytic ferments would also presumably neutralize any antiproteolytic influence of the fresh lymph.

Devising appropriate techniques, Wright soon found that the stale exudates of all the heavily infected wounds were in fact actively proteolytic; and that the fresh lymph from his "leeches" had an antiproteolytic effect, although usually somewhat less than that of serum.

It remained to show that, while normal serum (or lymph) with its full antiproteolytic power was a poor medium for the growth of microbes (because most of these could not utilize its unaltered proteins), it became a very good medium when sufficient proteolytic ferment was added to it to neutralize the antiproteolytic factor—or, better still, to make the serum actively proteolytic. By a simple experiment Wright and Fleming soon obtained clear evidence that this was the case. Taking a fresh sample of serum, they first estimated its proteolytic power, inoculated it with a gas-forming anaerobic bacillus, and then distributed it in equal volumes in miniature test-tubes. To each of these volumes (except one) they added increasing quantities of a proteolytic ferment (trypsin); and finally covered them all with melted petroleum jelly. The progressive increase of growth as the point was reached at which the antiproteolytic power was abolished and the fluid became actively proteolytic is well shown in Fig. 3.

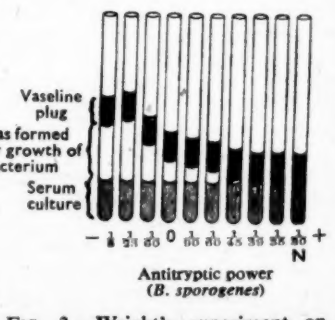
Vaseline plug
Gas formed by growth of bacterium
Serum culture
− 1 1/2 1/5 1/10 0 1/20 1/40 1/45 1/30 1/25 1/20 +
N
Antitryptic power
(B. sporogenes)

FIG. 3.—Wright's experiment on the antiproteolytic power of normal serum.

From this and similar experiments with other microbes it became clear that: (*a*) In normal serum, or lymph, with its full antiproteolytic power, very few of the microbic species found in war wounds (notably certain of the streptococci and staphylococci) can initiate growth and multiply fairly freely. Wright called these "serophytes." (*b*) Most of the species found in the war wounds cannot grow in normal serum or lymph until its antiproteolytic power has been blunted off or completely neutralized. Wright called these "serosaprophytes." (*c*) Some microbic species are intermediate between the above two classes.

Three Propositions

These findings gradually built themselves up in Wright's mind into a generalization which seemed to him, as it seems to me, of fundamental importance to our understanding of infectious diseases. It can perhaps best be formulated in the form of three distinct propositions. I cannot recall that Wright ever put it exactly in that way, but I think I do no violence to his ideas in so expressing it. The three propositions are these: (1) A microbe's capacity to initiate human disease is determined in part—an important part—by its capacity to multiply freely in human body fluids. (2) The capacity to multiply freely in human body fluids varies widely among the many microbic species which man encounters. (3) The capacity to multiply freely in body fluids is largely dependent upon reduction of the antiproteolytic power of the blood.

The first of these propositions may seem self-evident, yet, strangely enough, I have found no reference to it, or to the other two, in any textbook (in the English language) of pathology or of bacteriology or of medicine. But I suggest that there is much to support Wright's contention.

So far as our knowledge goes (there is room for further study of this point) there are only two microbic species which are able to multiply freely in human blood serum—namely, the haemolytic streptococcus and the staphylococcus. Is it an accidental coincidence that these two species have also caused such varied manifestations of human disease, and afflicted so many people in every part of the world? Consider first the haemolytic streptococcus—it has brought us scarlet fever, a formidable killer not long ago, and tonsillitis, and otitis media, with its heavy toll of deafness; it has brought us puerperal fever and rheumatic fever; countless septicaemias and disabilities resulting from wounds of war and of civil life; and it has proved a deadly complication of other disease, notably of influenza, as in the great pandemic of 1918, and of measles. The staphylococcus in its turn has brought us osteomyelitis, boils and carbuncles; much wound sepsis and many septicaemias; it has in the past added greatly to the heavy toll of smallpox and the misery of skin diseases; it has been responsible for many fatal respiratory infections of infants; for food-poisoning; and to-day it is still perhaps the most serious cause of cross-infection in hospitals.

May it not be that the ability of these two microbes to do so much damage to man is closely linked with their capacity to multiply freely in his body fluids? If that view is correct, surely Wright's generalization is one which pathology and medicine can ill afford to ignore. Even if his interpretation of his experimental facts was mistaken (which should certainly not be taken for granted) the facts themselves are of sufficient interest to warrant further investigation and discussion. And yet for nearly 40 years they have been completely ignored. I do not propose to consider here why that has happened. Suffice it to say that it is no new thing in science. It will be recalled that Mendel's classical work on inheritance attracted no attention for 35 years after his death; and that the same happened to Oliver Wendell Holmes's clear warning that puerperal fever was being transmitted by doctors and nurses. In our own time Fleming's suggestion that penicillin might be of value in medicine went almost unnoticed for more than 10 years, and, but for Florey's intelligent hunch that it was worthy of further investigation, we might still be without penicillin.

Experiments on the Properties of Leucocytes

To come back to the war wounds. When Wright had satisfied himself about the conditions which favoured proliferation of microbes in the wounds he turned his attention to the other side of the medal—the factors which check that proliferation and the invasion of tissues to which it so often gave rise. Naturally his thought focused on leucocytes. Surgeons had long speculated upon the part played by these cells in connexion with wound sepsis. Their possibly beneficial role was suggested by the term "laudable pus," but in sober fact there was still very little precise knowledge about the leucocytes and their functions. Wright set to work to study them as he might have done some new species of animal. Entirely new methods had to be devised for collecting leucocytes from blood; for observing their responses to microbes, to chemical agents, and to physical conditions. It amounted almost to a new chapter in physiology.

I will describe only two of his experimental procedures—which gave results so illuminating that they ought to be shown to every student. First what Wright called the "lath

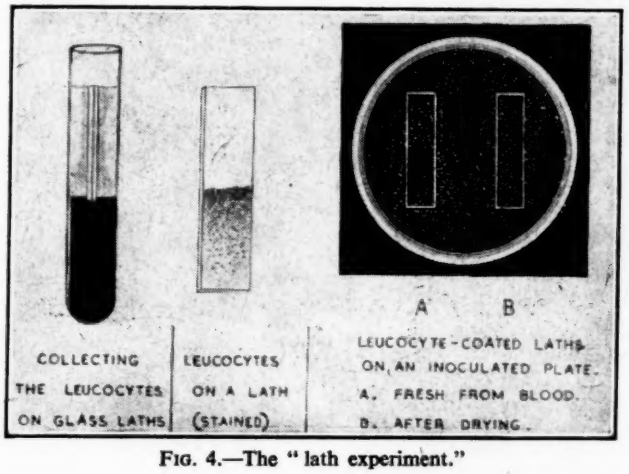

FIG. 4.—The "lath experiment."

experiment"—which demonstrated so clearly the remarkable capacity of leucocytes to restrain the growth of microbes such as staphylococci or streptococci. For this purpose two narrow strips of glass were placed back to back in a tube of quite fresh blood which was immediately centrifuged and then incubated for an hour (Fig. 4, left). During this incubation very large numbers of leucocytes left the blood clot and stuck on to the middle section of the two "laths," as could readily be seen by removing one of them from the blood, and washing and staining it (Fig. 4, centre). The other lath was then removed from the blood and placed, leucocyte-coated surface down, on an agar surface previously inoculated with staphylococci or streptococci. A third lath (from another tube of blood similarly treated) was removed from the blood and dried for half an hour in the incubator before being placed on the agar surface. In Fig. 4, right, it is evident that there has been a complete suppression of growth under the part of the undried lath where the leucocytes were most thickly massed. (In other experiments, conducted rather differently, it was shown that the microbes were completely killed by the cells.)

The second experiment was done with pus collected from a healing wound and was also intended to demonstrate the remarkable antimicrobic power of leucocytes (or their products). A drop of the pus was placed on a sterile agar surface and immediately covered with a portion of a microscope slide which, by its weight, pressed out the pus into a very thin layer. After incubation it was observed that no colonies had grown except at the extreme periphery of the drop of pus, where a few organisms had been squeezed out in the fluid, out of reach of the cellular elements (Fig. 5, A). Other samples of the same pus in which the leucocytes had

been put out of action—for example, by drying as at B, or by heating to 45° C. as at C—gave an abundant growth of colonies all through the specimen. Finally, in order to find out whether the pus could deal with a greater number of microbes than it originally contained, other drops were placed on a heavily infected agar surface (see lower half of Fig. 5). Under the drop of fresh untreated pus (at D) there was complete suppression of growth; while under the dried pus (at E) there was no suppression. We were unable by this method to arrive at the limit of the antimicrobic power of the leucocytes. Wright gave the name "bio-pyo-culture" to this type of experiment.

By these and many other ingenious experiments Wright contributed more, in my judgment, to our understanding of the factors at work in an infected wound than anybody else in the last 100 years. Again he had "made bacteriology" and also immunology.

As his work developed he was able to formulate the lines along which "treatment by physiological agencies" should proceed. In the early stages, he told the surgeons, the emphasis should be on the removal of foreign bodies and

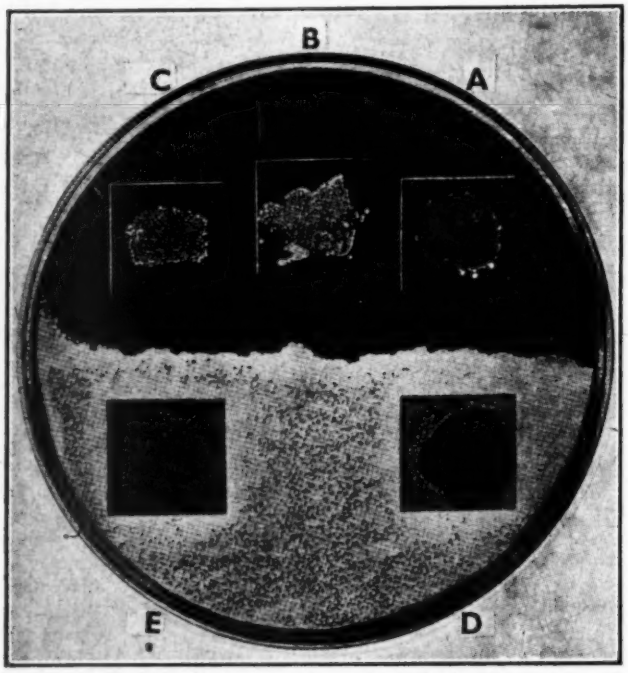

FIG. 5.—Experiment demonstrating the antimicrobic power of leucocytes.

necrotic tissues (since these would create "dead spaces") and on the promotion of an abundant flow of fresh lymph, rich in anti-proteolytic factor, to restrain the proliferation of microbes. In the later stages the emphasis should be on securing the best conditions for the functioning of leucocytes and on healing. "The leucocyte is the best antiseptic," he would say, and closure of the wound—by suture or skin-grafting—will usually give it the best conditions. In its essence, the present-day treatment of wounds finds its scientific basis in Wright's laboratory work during the first world war, although the textbooks of surgery tell the student nothing of that work.

I have spoken of only three points at which Wright broke new ground in medical science. There were of course many more. He was not greatly distressed that so much of his work failed to win general acceptance during his lifetime. He knew too well that the unconventional view is seldom popular, and he was confident that, in so far as he had found truth, his work would endure. "After all," he would say, "the Almighty is in no hurry; why should I be?"

Figs. 1, 2, and 3 are taken from Professor Fleming's paper in the *British Journal of Surgery*, 1919, **25**, 99; Fig. 5 from the paper by Almroth Wright in the *Lancet*, 1919, **1**, 489.

SERUM VITAMIN B_{12} CONCENTRATIONS OF PATIENTS WITH MEGALOBLASTIC ANAEMIA AFTER TREATMENT WITH VITAMIN B_{12}, FOLIC ACID, OR FOLINIC ACID

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The vitamin B_{12} concentrations in the serum and urine of normal subjects and of patients with untreated megaloblastic anaemia have already been reported (Mollin and Ross, 1952). Measurements of the vitamin were made by microbiological assay using *Euglena gracilis* var. *bacillaris* as test organism. The mean vitamin B_{12} concentration in the serum of normal subjects was found to be about 320 $\mu\mu$g. per ml.; the lower limit of the range in normal subjects was about 100 $\mu\mu$g. per ml. The concentrations in the serum of patients with untreated pernicious anaemia were below the normal range; the mean concentration was less than 40 $\mu\mu$g. per ml.

The changes in vitamin B_{12} concentrations in serum and urine during the first 72 hours after intramuscular injections of vitamin B_{12} have also been described. After the injections the concentrations of the vitamin in the serum of patients with pernicious anaemia rose from low pretreatment levels to within or above the normal range (Mollin and Ross, 1953).

In this paper we report the length of time that haemopoiesis was normoblastic and the serum vitamin B_{12} concentration was normal in patients with pernicious anaemia given single intramuscular injections of vitamin B_{12}—observations which have a direct bearing on the treatment of pernicious anaemia. In addition, the effect of daily injections of vitamin B_{12} and of treatment with folic acid or folinic acid is reported.

Materials and Methods

Observations are reported on 33 patients with pernicious anaemia in relapse and 13 patients suffering from other megaloblastic anaemias. While in hospital these patients received a diet from which meat was excluded and in which fish, butter, cheese, and eggs were restricted. Patients usually received the vitamin-B_{12}-deficient diet for five to seven days before treatment.

Method of Assay.—The method using *Euglena gracilis* var. *bacillaris* as test organism is based on that introduced by Hutner *et al.* (1949); details of the procedure followed have been described previously (Ross, 1952). Serum for assay purposes was usually taken daily; serial samples taken over a period of one to two weeks were generally assayed in one batch. All the samples were stored frozen and assayed at least twice. The concentrations recorded are total concentrations of vitamin B_{12} equivalent, but, as no significant amount of uncombined vitamin was present in the specimens

*In receipt of a grant from the Medical Research Council.

reported on, the total concentrations in fact also represent combined concentrations. A small number of abnormally high results thought to be due to the presence of some material which is haemopoietically inactive, but able to replace vitamin B_{12} in the growth of the test organism, have been omitted. The occurrence of such apparently non-specific results has been discussed previously (Mollin and Ross, 1952, 1953). Evidence that the Euglena assay is not completely specific for vitamin B_{12} has also been given by Robbins, Hervey, and Stebbins (1952), who found that the organism could grow in the presence of several pure substances which were inactive in the treatment of pernicious anaemia.

Bone-marrow Biopsy.—Serial samples of bone marrow were obtained from the sternum. Approximately 0.2 ml. of marrow was withdrawn into a dry syringe; smears were made immediately from the aspirated material. Air-dried films were stained with May–Grünwald Giemsa.

Serum Vitamin B_{12} Concentrations after Single Injections of the Vitamin

Injections of 20, 40, 80, 160, 320, or 1,000 μg. of crystalline vitamin B_{12} were given to pernicious-anaemia patients. Thirty injections were given to patients who were in relapse and who had received no treatment for at least six months. Seven injections were given to patients who had previously received treatment but in whom the serum vitamin B_{12} concentration had again fallen to low levels and in whom haemopoiesis was once more megaloblastic. The serum vitamin B_{12} concentrations in these patients were measured at frequent intervals, usually daily. Daily blood counts and reticulocyte counts were also made. Marrow biopsies were carried out at frequent intervals in most patients. The amount of vitamin B_{12} excreted in the urine after injections of the vitamin was also measured in most instances. Some of these observations are summarized in Table I; detailed observations on certain of the patients are given below.

Relation Between Serum Vitamin B_{12} Concentration and Haemopoiesis

In Fig. 1 is illustrated an example of the type of study made. This patient (Case 7) was given an initial injection of 80 μg. of vitamin B_{12}, followed 20 days later by an injection of 160 μg. Before treatment the serum vitamin B_{12} concentration was low (55 $\mu\mu$g. per ml.); after the first injection of 80 μg. it remained above the lower limit of the normal range (100 $\mu\mu$g. per ml.) for 11 days. The bone marrow was normoblastic while the serum concentration was normal, but was found to have undergone intermediate megaloblastic change within a few days of the level falling below 100 $\mu\mu$g. per ml. After the injection of 160 μg. the serum vitamin B_{12} concentration remained normal for a further 21 days.

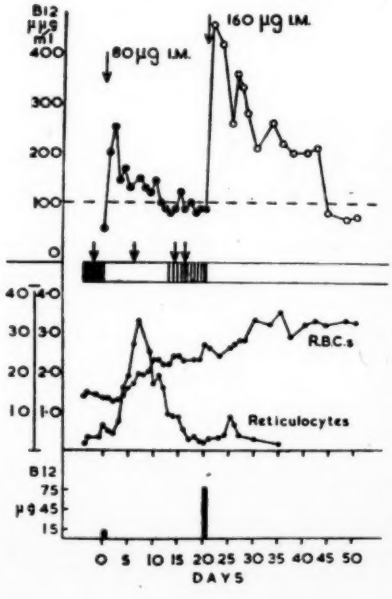

FIG. 1.—Changes in serum and urine vitamin B_{12} concentrations, in bone marrow, and in blood count of a patient with pernicious anaemia after intramuscular injections of 80 μg. and 160 μg. of vitamin B_{12}. (The changes in the marrow are shown diagrammatically in Figs. 1–5. The black area represents megaloblastic haemopoiesis, the vertically lined area represents intermediate megaloblastic haemopoiesis, and the open area represents normoblastic haemopoiesis. The arrows indicate the times of marrow biopsy.)

In Fig. 2 are illustrated examples of the relation between the serum vitamin B_{12} concentration and haemopoiesis in patients with untreated pernicious anaemia following injections of 20 μg. of vitamin B_{12}. Early megaloblastic change was recognized in the bone marrow a few days after the serum vitamin B_{12} concentration fell below 100 $\mu\mu$g. per ml.; at levels greater than this the marrow remained normoblastic.

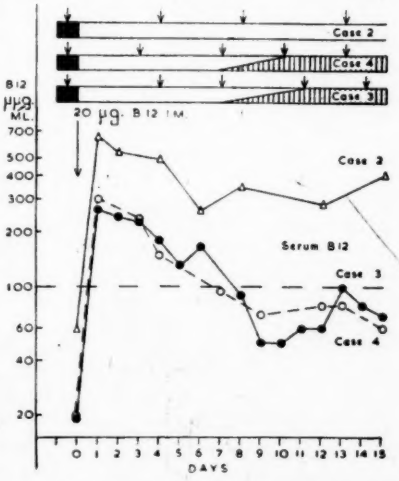

FIG. 2.—Serum vitamin B_{12} concentrations and bone-marrow changes in three patients with pernicious anaemia after intramuscular injections of 20 μg. of vitamin B_{12}.

Similar observations were made on 15 other patients given injections of 20, 40, 80, 160, 320, or 1,000 μg. In all the patients, when the marrows were normoblastic (53 observations) the serum vitamin B_{12} concentrations ranged from 80 to 860 $\mu\mu$g. per ml., with a mean concentration of 250 $\mu\mu$g. per ml.; when they were megaloblastic (28 observations) the concentrations ranged from 50 to 120 $\mu\mu$g. per ml., with a mean concentration of 83 $\mu\mu$g. per ml., except in one patient. This patient, a woman aged 70, who was greatly neglected and before admission had been taking a diet deficient in both folic acid and ascorbic acid, responded well initially to an injection of 160 μg. of vitamin B_{12}, but showed early signs of relapse in the bone marrow when her serum vitamin B_{12} level was still about 200 $\mu\mu$g. per ml.

Duration of Normal Serum Vitamin B_{12} Concentrations after Injections: Relation to Amounts of Vitamin Retained in Body

In Table I is shown the length of time during which the vitamin B_{12} concentrations of the serum of patients with pernicious anaemia remained at or above 100 $\mu\mu$g. per ml. after intramuscular injections of vitamin B_{12}. There was considerable variation in the duration in patients given the same dose of the vitamin, but on the average the concentration remained within the normal range for longer periods after larger injections. In Table I is also shown the amount of vitamin retained after intramuscular injections, calculated by subtracting the amounts of vitamin B_{12} recovered in the urine in the first 24 hours after injections from the amount given. The average time the levels remained within the normal range increased significantly in proportion to the amount of the vitamin retained in the body. However, the differences in duration of normal levels in individual patients could not be entirely explained by differences in retention of the vitamin (see Discussion).

It must be emphasized that the serum vitamin B_{12} levels of patients with pernicious anaemia, although within the normal range for days or weeks after single injections of the vitamin, were usually much lower than the levels found in normal subjects. Even 24 hours after the injections of 40 μg. the mean serum concentration was well below the mean normal level of 322 ± 29 $\mu\mu$g. per ml. (Mollin and Ross, 1952). After injections of 80 or 160 μg. the mean serum concentrations were as high as the mean normal level only for the first four days (see Table II).

TABLE I.—*Duration of Normal Serum Vitamin B_{12} Levels and Normoblastic Haemopoiesis in Patients with Pernicious Anaemia after Intramuscular Injections of Vitamin B_{12}, together with the Amount of the Vitamin Retained*

Case No.	Pre-treatment R.B.C. (mil./c.mm.)	I.M. Dose of Vitamin B_{12} (μg.)	Vitamin B_{12} Retained* (μg.)	Duration of Serum Vitamin B_{12} above 100 $\mu\mu$g. per ml. (Days)	Bone Marrow†	
					Normoblastic (Days)	Megaloblastic (Days)
1	1·6	20	—	11	7	10
4a	1·8	20	—	6	7	10
3	2·0	20	—	7	7	11
2	2·4	20	—	18+	14	—
8	3·1	20	—	7	—	—
4b	3·2	20	—	8	—	8
9	3·3	20	—	8	—	—
10a	1·3	40	34	2	—	3
11	1·5	40	39	8	—	15
12	1·5	40	37	16	14	18
13	2·0	40	37	7	9	11
14	3·2	40	34	22	—	20
15	4·2	40	—	11	—	—
16	1·1	80	58	11	17	21
6	1·2	80	76	27+	23	—
7a	1·3	80	67	11	—	14
17	1·3	80	75	33+	22	—
18	1·3	80	71	24+	3	16
5	2·4	80	71	35+	29	—
19	3·2	80	53	19	—	—
20	3·7	80	63	17	5	—
21	3·7	80	65	32	7	—
22	1·2	160	92	23	24	35
23	1·4	160	—	48	24	49
24	1·5	160	125	29+	26	—
10b	1·6	160	39	11	10	12
7b	2·7	160	72	21	—	—
25a	2·8	160	72	19	—	—
26	3·7	160	97	22	9	—
10c	2·5	320	—	39	25	—
27	2·5	320	124	50+	—	—
25b	4·0	320	255	98	—	—
10d	2·9	1,000	410	51+	—	—
29	2·8	1,000	220	34	7	67
30	3·6	1,000	190	58	—	66
28a	1·9	40 Liver extract	36	17	14	—
28b	2·8	40 Liver extract	37	14+	—	—

* The difference between the dose given and the amount of vitamin found in the urine in the first 24 or 48 hours. In most instances, except with the largest doses, excretion was complete within 24 hours.

† The normoblastic figures are the times of the last marrow biopsy showing normoblastic haemopoiesis. The megaloblastic figures are the times of the first marrow biopsy showing megaloblastic haemopoiesis.

TABLE II.—*Mean Serum Vitamin B_{12} Concentrations in Patients with Pernicious Anaemia Before and After Intramuscular Injections of Vitamin B_{12}*

I.M. Dose of Vitamin B_{12}	Mean Serum Vitamin B_{12} Concentrations ($\mu\mu$g. per ml.)*					
	Pre-treatment†	Post-treatment: Days after Injections				
		1–2	3–4	5–6	7–8	9–10
40 μg.	38±2·2 (60)	181± 29 (11)‡	134± 15 (10)	141±29 (10)	151±41 (9)	94± 8 (8)
80 μg.	40±2·5 (48)	320± 34 (16)	245± 36 (13)	265±33 (12)	207±42 (12)	206±34 (14)
160 μg.	45±3·3 (52)	367± 54 (12)	307± 58 (11)	225±23 (11)	196±22 (12)	165±26 (11)
320 μg.	52±7·2 (8)	698±352 (4)	485±165 (2)	200 (1)	377±76 (2)	360±44 (2)

* Nine pretreatment results (125 to 1,600 $\mu\mu$g. per ml.) and five post-treatment results (460 to 2,000 $\mu\mu$g. per ml.) were excluded because the values found were considered not to represent true serum vitamin B_{12} concentrations.

† The true mean was lower than the stated mean because the values in some sera were too low to be measured.

‡ Number of observations from which the mean is calculated.

Serum Vitamin B_{12} Concentrations after Daily Injections of the Vitamin

In Fig. 3 are compared the effect of daily injections of 1 μg. and that of 40 μg. of vitamin B_{12} given respectively to two patients with pernicious anaemia. The serum vitamin B_{12} concentrations were assayed 24 hours after each injection immediately before the next injection was given. The levels rose to within the normal range 24 hours after the first injection of 40 μg.; they then increased steadily, reaching after 10 days of treatment a level of approximately 1,000 $\mu\mu$g. per ml., this level being maintained as long as the daily injections were given. The vitamin B_{12} concentration of the serum of the patient given 1 μg. daily was not consistently within the normal range—that is, more than 100 $\mu\mu$g. per ml.—until 15 days after treatment started.

Although there was a great difference in the serum vitamin B_{12} levels following these regimes, the differences in the haematological responses were less dramatic. Erythropoiesis in the bone marrow of both patients was normoblastic by the seventh day. The initial red-cell increase was more rapid in the patient given the larger injections, but after the fifteenth day the rate of increase was almost the same.

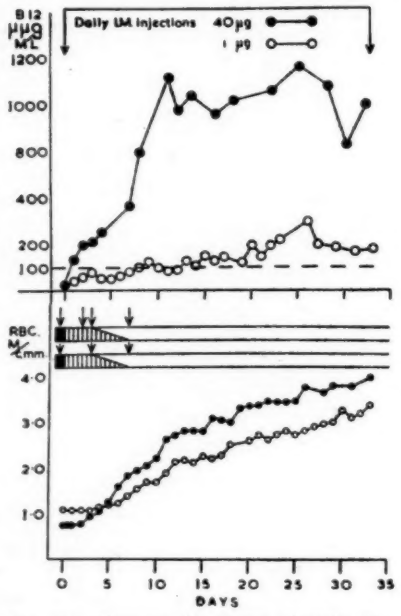

FIG. 3.—Changes in serum vitamin B_{12} concentration, bone marrow, and red-cell count of two patients with pernicious anaemia who received daily injections of vitamin B_{12}.

In another patient given 1,000 μg. daily the serum vitamin B_{12} concentration 24 hours after each injection reached and maintained a level of about 1,300 $\mu\mu$g. per ml. after seven days of treatment.

Serum Vitamin B_{12} Concentrations of Patients Treated with Folic Acid or Folinic Acid

In Megaloblastic Anaemia due to Vitamin B_{12} Deficiency.—The serum vitamin B_{12} concentrations of patients with megaloblastic anaemia due to vitamin B_{12} deficiency remained low when these patients were treated with folic acid by mouth or folinic acid by intramuscular injection.

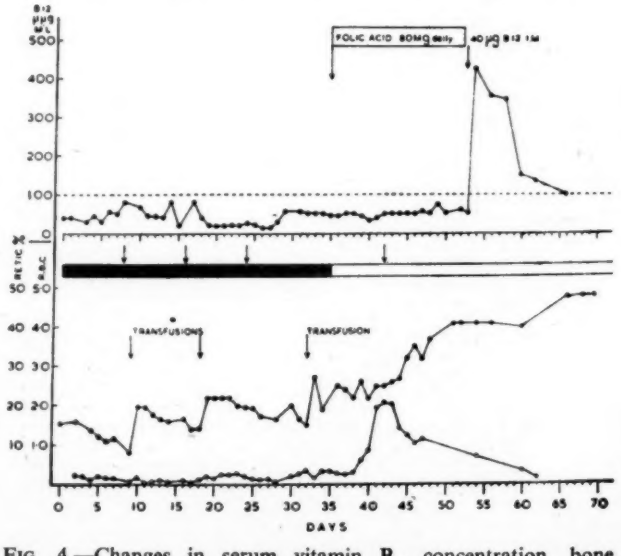

FIG. 4.—Changes in serum vitamin B_{12} concentration, bone marrow, and blood count of a patient with pernicious anaemia (Case 15) after folic acid by mouth followed by vitamin B_{12} by injection.

In Fig. 4 are illustrated the haematological response and the serum vitamin B_{12} concentrations of a patient with pernicious anaemia who was treated first with ineffective preparations of vitamin B_{12} and gastric juice by mouth, then with folic acid and finally with vitamin B_{12}. Similar observations were made on a patient whose megaloblastic anaemia was due to vitamin B_{12} deficiency developing as a result of an ileocolostomy performed to relieve obstruction due to multiple strictures of tuberculous origin. This patient was treated with injections of folinic acid and then with folic acid by mouth.

In Megaloblastic Anaemias due to Deficiency of Folic Acid.—Twelve patients with megaloblastic anaemias associated with the sprue syndrome and/or pregnancy had serum vitamin B_{12} concentrations within the normal range before treatment and failed to respond to treatment with vitamin B_{12}. These patients responded to folic acid by mouth or to folinic acid by intramuscular injection; their serum vitamin B_{12} levels remained normal during their responses to treatment. In Fig. 5 are illustrated the changes in the blood count and serum vitamin B_{12} concentration and bone marrow of one of these patients. She was suffering from steatorrhoea associated with severe pulmonary tuberculosis, and was treated first with vitamin B_{12} and then with folinic acid.

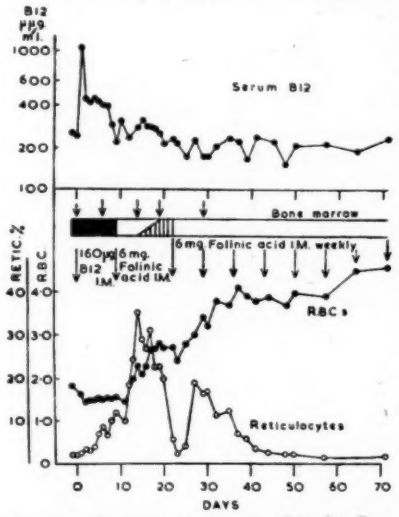

FIG. 5.—Changes in serum vitamin B_{12} concentration, bone marrow, and blood count of a patient with steatorrhoea.

Discussion

Serum Vitamin B_{12} Concentration and Haemopoiesis

In a previous communication (Mollin and Dacie, 1950) it was pointed out that the recognition of the reappearance of early ("intermediate") megaloblastic change in the marrow of patients with pernicious anaemia treated with liver extract or vitamin B_{12} was a sensitive method for determining the time of onset of relapse in these patients. In this paper the changes in haemopoiesis have been correlated with the changes in serum vitamin B_{12} concentration.

While the serum vitamin B_{12} level of patients with uncomplicated pernicious anaemia was within the normal range after injections of the vitamin, haemopoiesis was normoblastic, but when the level fell consistently below the normal range megaloblastic change reappeared in the bone marrow. These findings confirmed our earlier observations that a serum level of around 100 $\mu\mu$g. per ml. was the critical concentration below which signs of vitamin-B_{12} deficiency became recognizable (Mollin and Ross, 1952). However, when very small daily injections of 1 μg. were given to one patient (Fig. 3), the bone marrow was normal by the sixth day, although the serum level 24 hours after each injection was not consistently raised above 100 $\mu\mu$g. per ml. until 15 days after treatment began. Presumably immediately after each injection the serum level became high enough for the marrow to become normoblastic even though there was not enough vitamin B_{12} in the body to keep the serum level above 100 $\mu\mu$g. per ml. throughout the 24 hours after each injection. In fact, it was found in another patient that the serum vitamin B_{12} level rose above 100 $\mu\mu$g. per ml. in the first three hours after a single intramuscular injection of 1 μg. of vitamin B_{12}.

Following the single larger injections of vitamin B_{12} the actual serum level at which megaloblastic change again became recognizable varied. In a few patients the marrow was normoblastic when the serum concentration was as low as 80 $\mu\mu$g. per ml., while in some others the marrow was beginning to show megaloblastic change when the level was as high as 120 $\mu\mu$g. per ml. This is not surprising in view of the probable natural variability in sensitivity of the patients to deficiency of the vitamin and the experimental error of the assay method. Furthermore, the early stages of reversion towards megaloblastic haemopoiesis may not be easy to recognize. This reversion was more pronounced and more easily recognizable in severely anaemic patients given the smaller injections (20 and 40 μg.). In others, signs of reversion were confined to the appearance of a variable proportion of intermediate megaloblasts and abnormal granulocytes. The presence of abnormal granulocytes was useful as an indication of relapse only if leucopoiesis had previously been restored to normal.

Effect of Folic Acid, Folinic Acid, and Vitamin C

The serum vitamin B_{12} levels of the patients with pernicious anaemia in relapse remained low while they were treated with folic acid or folinic acid, though haemopoiesis in their marrow rapidly became normoblastic. The serum levels of patients with megaloblastic anaemia who failed to respond to treatment with vitamin B_{12} were normal before treatment and were not changed by treatment with either folic acid or folinic acid. Therefore the amount of folic acid or folinic acid available for haemopoiesis greatly affects the relation between the serum vitamin B_{12} level and the type of haemopoiesis. The amount of vitamin C available may also affect this relation. In 1942 Dyke, Della Vida, and Delikat claimed that if vitamin C was deficient in the diet of patients with pernicious anaemia the patients might fail to respond to treatment with liver extract. More recently it has been suggested that vitamin C may be concerned in the utilization of folic acid, perhaps by aiding its conversion to folinic acid (Nichol and Welch, 1950; May *et al.*, 1951).

These factors, folic acid and vitamin C, may influence the relation between the serum vitamin B_{12} level and haemopoiesis in two ways. First, if there is severe dietary deficiency of either, megaloblastic haemopoiesis may be present in spite of an adequate vitamin B_{12} level in the serum. A possible example of this has been mentioned earlier in the section on the effect of single injections of vitamin B_{12}. Secondly, if unusually large amounts of folic acid are available, or if it is more efficiently utilized in the presence of ample amounts of vitamin C (Nichol and Welch, 1950), the serum vitamin B_{12} level might be low, though the marrow might be almost normal and the anaemia slight or absent. Patients with pernicious anaemia occasionally have neurological complications but little or no anaemia. The marrows of such patients show early signs of megaloblastic change. The few patients of this type that we have seen have had definitely low serum vitamin B_{12} levels—less than 50 $\mu\mu$g. per ml.—lower than would be expected from the degree of megaloblastic change and anaemia present. It is possible that these patients absorb sufficient folic acid to maintain normal or almost normal haemopoiesis, or utilize the available folic acid more efficiently.

The patients we treated with folic acid did not develop subacute combined degeneration; however, they were treated for short periods only (Fig. 4). If this treatment had been continued, the serum vitamin B_{12} level might have fallen to lower levels with consequent neurological changes.

Duration of Normal Serum Vitamin B_{12} Concentrations after Injections

Though there was considerable variation in the duration of normal vitamin B_{12} levels in different patients given the same dose of vitamin B_{12}, the average duration was longer after the larger injections (Table I). After injections of 20 μg. the serum concentrations fell below the lower limit of the normal range before the tenth day in most patients.

After injections of 40 μg. the level became subnormal before the twenty-second day in all patients, the average duration being 11 days. There was no clear-cut difference in the duration of normal levels after injections of 80 and 160 μg., but some difference would presumably have been demonstrated if larger numbers of patients had been treated. The serum vitamin B_{12} levels of most patients given 80 and 160 μg. were subnormal by the twenty-eighth day, but the serum concentrations of several remained within the normal range for longer than 35 days. The few patients given larger injections (320 and 1,000 μg.) maintained normal serum levels for longer periods. The serum levels of nearly all these patients, although falling below 100 μμg. per ml. in the times stated, were, however, higher than before treatment for at least as long again.

The observations of Walker and Hunter (1952) suggest that when single injections of 1,000 μg. of vitamin B_{12} are given to patients with pernicious anaemia in relapse signs of reversion appear in the marrow of most of them in from 76 to 140 days. In our patients signs of reversion appeared earlier, see Table I.

Injections of Liver Extract.—The duration of normal serum vitamin B_{12} levels in a few patients who received injections of liver extract of known vitamin B_{12} content was similar to that after equivalent doses of crystalline vitamin B_{12} (Table I). We have previously reported that the changes in the serum levels in the first 72 hours after injections of liver extract and of crystalline vitamin B_{12} were similar (Mollin and Ross, 1953).

Relation of Serum Vitamin B_{12} Level to Body Stores of Vitamin B_{12}

It is surprising how effective injections of vitamin B_{12} are in maintaining the serum levels, in view of the extent to which the tissues of patients with pernicious anaemia in relapse are depleted of the vitamin. The observations of Girdwood (1952) suggest that the tissues of normal subjects may contain at least 1,000 to 2,000 μg. of vitamin B_{12} as estimated by the *Lactobacillus leichmannii* assay. He could detect very little or no vitamin B_{12} in the tissues of patients with pernicious anaemia in relapse. Drouet, Wolff, Karlin-Weissman, and Rauber (1951) and Wolff, Drouet, and Karlin-Weissman (1951) found that the average concentration of growth factors for *L. leichmannii* in the livers of patients with pernicious anaemia in relapse was not more than 0.06 μg. per g. This concentration was less than one-tenth of that of control subjects, who may store about 1,000 μg. of vitamin B_{12} in their liver. Single injections of 20 and 40 μg. of vitamin B_{12} obviously could do very little to restore the depleted reserves of vitamin B_{12} in patients with pernicious anaemia in relapse; yet such injections raise the vitamin B_{12} level in the serum to within the normal range for a number of days (see Tables I and II). This suggests that all available vitamin B_{12} in the body is mobilized to maintain a normal serum level as long as possible in order to supply essential requirements; a total of less than 1 μg. throughout the plasma is enough to give a normal concentration (Mollin and Ross, 1953).

Table II shows that really normal levels—that is, 320± 29 μμg. per ml.—were maintained for some days only after the larger single injections, such as 320 μg., although injections of as little as 1 μg. daily for 15 days were enough to raise the level to just above the lower limit of the normal range (see Fig. 3).

It would appear, therefore, that the serum vitamin B_{12} level can be maintained within the normal range with very little vitamin B_{12} in store, whereas a much larger amount in store is needed to keep the serum level at the mean normal concentration. Presumably only when the stores of vitamin B_{12} are almost completely exhausted does the serum level fall below the normal range and signs of a megaloblastic anaemia develop.

The tissues of patients in mild relapse, though severely depleted of the vitamin, are presumably less depleted than those of patients in severe relapse. The serum vitamin B_{12} levels of patients with mild relapse, though below 100 μμg. per ml., were rather higher than those of patients with severe relapse (Mollin and Ross, 1952). This may be due to greater stores of the vitamin. We were, however, unable to demonstrate that the duration of normal serum vitamin B_{12} levels was significantly related either to the initial serum level or to the initial red-cell count. However, in certain patients whose pretreatment serum vitamin B_{12} levels were only moderately low—between 60 and 100 μμg. per ml.—the duration of normal levels and the actual height maintained were much greater than the average (see Fig. 2, Case 2).

Implications for Treatment

From the study of bone marrows and serum vitamin B_{12} levels it appears that the average size of injection of vitamin B_{12} required to maintain the marrow normoblastic and the serum level within the normal range, at least during the initial period of the treatment, would be 20 μg. of vitamin B_{12} every 7 days, 40 μg. every 10 days, or 80 to 160 μg. every 15 to 28 days. Some patients require more; others require less. However, it is doubtful if treatment would be adequate if the dose of vitamin B_{12} was restricted to these amounts. At best such doses represent the average amounts required to prevent the appearance of signs of deficiency. It has already been suggested that vitamin-B_{12} deficiency must be extreme before the serum level falls below the normal range and before signs of megaloblastic change appear in the developing haemopoietic cells. Though the blood count usually becomes normal and is maintained at a normal level with the dose regimes mentioned, the tissues probably contain little or no reserve of the vitamin for months or even years after the start of treatment. Nevertheless, the depleted tissue reserves can probably be restored if enough vitamin B_{12} is given during the initial stages of treatment. Drouet *et al.* (1951) found that the concentration of vitamin B_{12} in the liver of patients with pernicious anaemia increased following intramuscular injections of the vitamin, and Girdwood (1952) found vitamin B_{12} in the liver and kidneys of a patient with pernicious anaemia who died shortly after an injection of vitamin B_{12}.

It has already been mentioned that in health the body reserves of vitamin B_{12} may amount to from 1,000 to 2,000 μg. Therefore, if the aim at the beginning of treatment of a patient with pernicious anaemia is to restore to normal the vitamin B_{12} reserve, the total dosage given must ensure the retention in the body of at least this amount. To accomplish this it may be necessary to give a total of as much as 5,000 μg. by injection. Believing it is desirable to replenish the body stores, we found it convenient to give five injections of 1,000 μg. (1 mg.), dissolved in 1 ml. of diluent, in the first week or two of treatment. Of such a dose a large proportion is excreted, but, from the results of assays of the amounts passed in the urine (Chesterman, Cuthbertson, and Pegler, 1951; Mollin and Ross, 1953) and from the long duration of the clinical effect, it would appear that about 200 to 300 μg. of each injection may be retained in the body. Although smaller doses are less wasteful, the more frequent injections required are less convenient. Thereafter injections of 40 to 60 μg. fortnightly or 80 to 100 μg. monthly should be more than enough to maintain the reserves. Large initial doses of liver extract were recommended by Askey (1941) in order to restore the liver reserves of the anti-pernicious-anaemia factor, but the large dosage required can be much more satisfactorily given by means of injections of crystalline vitamin B_{12}.

The observations reported in this paper support the view that the manifestations of pernicious anaemia are primarily due to deficiency of vitamin B_{12}. Conditioned deficiencies of folic acid or ascorbic acid may be present when the deficiency of vitamin B_{12} is severe (Spray, Fourman, and Witts, 1951; Wallerstein, Harris, and Gabuzda, 1952). However, treatment with these substances does not seem to be required provided the patients are taking a good diet and are given adequate amounts of vitamin B_{12}.

Summary

The serum vitamin B_{12} concentrations of patients with pernicious anaemia in relapse rose from low pretreatment levels to within the normal range after single intramuscular injections of 20 to 1,000 μg. of vitamin B_{12}. Concentrations were within the normal range for from 6 to more than 18 days after injections of 20 μg.; from 2 to 22 days after 40 μg.; from 11 to at least 35 days after 80 μg.; from 11 to at least 48 days after 160 μg.; from 39 to 98 days after 320 μg.; and from 34 to at least 58 days after 1,000 μg.

Although the concentrations were within the normal range for these periods, the mean of the concentrations of all the patients in each treatment group fell within a few days of the injections below the mean concentration found in normal subjects.

When the serum vitamin B_{12} concentrations were normal haemopoiesis was normoblastic; when the concentrations were below the normal range megaloblasts reappeared in the marrow.

Intramuscular injections of 40 μg. of vitamin B_{12} every 10 days, or of 160 μg. every 21 days, maintained the serum vitamin B_{12} level of most patients with pernicious anaemia within the normal range. These doses seem to be the minimum requirement for the treatment of most patients with pernicious anaemia in relapse. It is recommended, however, that much larger doses of vitamin B_{12} (up to 5 mg.) should be given in the first week or two of treatment in order not only to supply enough vitamin B_{12} for haemopoiesis but also to replenish the greatly depleted tissue reserves.

The serum vitamin B_{12} concentrations of patients with various megaloblastic anaemias were not altered by treatment with folic acid or folinic acid.

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VITAMIN B_{12} IN NUTRITIONAL MACROCYTIC ANAEMIA

BY

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The efficacy of vitamin B_{12} in pernicious anaemia (P.A.) and its neurological complication is now well established. The exact status of vitamin B_{12} in the treatment of nutritional macrocytic anaemia (N.M.A.) is, however, still uncertain owing to the scarcity of available reports. Folic acid is universally held to be the drug of choice in N.M.A. The present communication deals with trials of vitamin B_{12} in 22 cases of N.M.A. undertaken to find out primarily its value in N.M.A., and incidentally to compare its haematinic efficiency with that of folic acid and/or liver extract.

Materials and Methods

The patients were all Indians. Only uncomplicated cases admitted into hospital were chosen for this study. Vitamin B_{12} was started only when the blood picture had stabilized after admission. In most cases it was administered intramuscularly; in a few cases it was taken orally in tablet form. A course usually lasted for three to five consecutive days. A second and sometimes a third course were given when the improvement was not adequate or sustained—that is, when the blood values either became stationary or dropped after initial improvement. Folic acid was given orally in doses of 30 mg. a day when there was no improvement with vitamin B_{12} or when the improvement was not sustained. Finally, crude liver extract was given in doses of 3 to 4 ml. a day for six to ten days when the improvement with folic acid was found to lag. Ferrous sulphate, 18 to 21 gr. (1.2 to 1.4 g.) a day was given when hypochromicity was noted after treatment with vitamin B_{12}.

During the whole period the patients had an identical diet consisting of 8 oz. (225 g.) rice, 2 oz. (56 g.) peas, 4 oz. (113 g.) potatoes, 8 oz. green vegetables, 4 oz. bread, 2 oz. butter, 2 oz. sugar, 16 oz. (450 g.) milk, 4 oz. fish, 1 lime, 1 banana. This diet, which is relatively poor in animal protein, has been found to have no haemopoietic activity in N.M.A. A high-protein diet has distinct haemopoietic activity in N.M.A. (Das Gupta and Chatterjea, 1951), and it is therefore imperative that in the evaluation of the efficacy of different haematinics the patients be always on a control diet as above.

The degree of improvement after each course of treatment has been calculated according to the formula of Della Vida and Dyke (1942); for working purposes the improvement rate is indicated as follows:

Very good	=	improvement	rate	over	90%
Good	=	,,	,,	between	75 and 90%
Very fair	=	,,	,,	,,	50 ,, 74%
Fair	=	,,	,,	,,	30 ,, 49%
Tolerable	=	,,	,,	,,	15 ,, 29%
Nil	=	,,	,,	below	15%

Dosage.—Vitamin B_{12} was not given in graded dosage, the amount usually being determined by the supplies at our disposal. Thus at the beginning, when we had only a limited supply, small doses were used, while during the later part we had liberal supplies and large doses were given.

Bone Marrow.—All cases in the series had cellular megaloblastic bone marrow.

Details of the cases and the results of treatment are shown in Table I.

Vitamin B_{12} Parenterally

In 21 cases of N.M.A. vitamin B_{12} was administered intramuscularly, the total amount given to any single case ranging from 30 to 600 µg. in one, two, or three courses of treatment. Six of these cases were also treated orally, five before and one after parenteral therapy. The maximum improvement in each case after a course of parenteral vitamin B_{12} is shown in Table II. Though the improvement was very good in ten cases, good in four, and fair in four, it was sustained in four cases only.

A second course of treatment was given in 12 cases—in six (Nos. 1, 3, 6, 7, 10, and 15) the response was increased, in four (Nos. 4, 8, 9, and 13) it was equal, and in two (Nos. 12 and 14) it was decreased compared with the previous course. Two cases (Nos. 10 and 15) had a third course, and in each the response was less than with the previous course.

Correlation of the improvement index with the dose of vitamin B_{12} is shown in Table III. There was great variation in response in different patients and in the same patient at different times. Strict correlation was not seen between the dose of vitamin B_{12} and the improvement index, though a better response was usually noted after a large dose—240 µg. or more. Continuation of treatment produced

TABLE I.—*Details of Haematological Response at Days Indicated*

Case No.	Age and Sex	Haematinic	Route	Dose			Day* of Treatment	Hb (g./%)	R.B.C. (mil./c.mm.)	M.C.V. (m.³)	Retics.		I.R.†	Remarks
				Daily	No. of Days	Total					%	Day		
1	30 M	Vit. B_{12}	I.M.	10 µg.	3	30 µg.	0	3·48	1·01	148·5	10·2	8		Hypochlorhydria.
							15	4·93	1·23	146·3			Tol.	Blood values reached normal without
							20	6·96	1·74	143·6				further treatment
		,, ,,	I.M.	20 µg.	2	40 µg.	15	10·15	2·75	123·6			V.G.	
							42	13·48	4·06	98·5				
2	25 M	Vit. B_{12}	I.M.	20 µg.	6	120 µg.	0	2·03	0·52	173·0	12·8	7		Hypochlorhydria.
							15	7·54	2·04	121·5			V.G.	Blood values reached normal without
							20	7·54	2·01	124·0				further treatment
		Folic acid	Oral	30 mg.	20	600 mg.	15	10·44	3·14	108·2			V.G.	
							21	10·73	3·21	102·8				
		Liver ext.	I.M.	4 ml.	6	24 ml.	14	1·89	3·75	96·0			V.G.	
3	45 M	Vit. B_{12}	Oral	5 µg.	6	30 µg.	0	7·25	1·66	120·4				Isochlorhydria.
							15	7·25	1·65	139·3			Nil	Blood values reached normal level
		,, ,,	I.M.	5 µg.	6	30 µg.	0				11·8	6		with more vit. B_{12}
							15	10·44	2·50	136·0			V.F.	
							21	10·44	2·48	133·1				
		,, ,,	I.M.	20 µg.	6	120 µg.	15	12·47	3·77	103·4	2·1	4	V.G.	
4	28 M	Vit. B_{12}	I.M.	40 µg.	5	200 µg.	0	3·48	0·73	137·0	7·4	6		Isochlorhydria
							15	7·54	2·21	117·6			V.G.	
							20	9·28	2·62	129·7				
							25	9·28	8·29	110·7				
		,, ,,	I.M.	20 µg.	5	100 µg.	10	11·60	3·68	103·2				
							15	11·81	3·95	101·2			V.G.	
		Folic acid	Oral	30 mg.	15	450 mg.	15	12·75	4·30	97·6			V.G.	
5	22 M	Vit. B_{12}	I.M.	40 µg.	6	240 µg.	0	2·90	0·71	154·9	11·5	5		Hypochlorhydria.
							15	7·83	2·34	123·9			V.G.	
							20	8·70	2·20	127·2				
		Folic acid	Oral	30 mg. 20 mg.	13 8	550 mg.	15	10·73	3·19	109·7			V.G.	
							25	11·02	3·23	108·3				
		Liver ext.	I.M.	3 ml.	10	30 ml.	15	12·49	3·73	101·9			V.G.	Left hospital
6	60 M	Vit. B_{12}	I.M.	45 µg.	3	120 µg.	0	4·93	1·24	137·1	6·3	4		Hypochlorhydria.
							15	8·55	2·27	127·8			G.	
							25	8·70	2·60	107·6				
		,, ,,	I.M.	40 µg. 50 µg.	3 2	220 µg.	15	11·02	3·31	105·7			V.G.	
							25	11·02	3·12	112·1				
		Folic acid	Oral	30 mg.	15	450 mg.	7	12·18	3·54	104·5				
							15	12·18	3·58	103·3			G.	Left hospital
7	32 F	Vit. B_{12}	I.M.	40 µg.	3	120 µg.	0	5·22	1·15	165·2	12·1	7	F.	Hypochlorhydria.
							15	6·67	1·63	147·2				Blood picture
		,, ,,	I.M.	40 µg.	3	120 µg.	10	7·83	2·38	126·0			V.G.	changed to dimorphic type and further improvement was noted after iron and liver extract
8	56 F	Vit. B_{12}	Oral	100 µg.	5	500 µg.	0	4·35	1·15	139·3	15·6	6		Isochlorhydria
							7	5·22	1·23	162·5			Nil	
		,, ,,	I.M.	50 µg.	5	250 µg.	15	8·41	2·49	128·5	13·2	4	V.G.	
							21	9·86	2·83	120·1				
		,, ,,	I.M.	50 µg.	6	300 µg.	15	11·60	4·07	95·8			V.G.	
9	57 M	Vit. B_{12}	Oral	100 µg.	5	500 µg.	0	5·22	1·36	125·0	Nil			Hypochlorhydria
							7	5·22	1·09	146·7			Nil	
		,, ,,	I.M.	50 µg.	5	250 µg.	15	8·41	2·31	125·5	13·6	7	V.G.	
		,, ,,	I.M.	50 µg.	6	300 µg.	15	10·73	3·22	111·8			V.G.	
							30	13·05	4·11	102·1				
10	23 F	Vit. B_{12}	I.M.	40 µg.	5	200 µg.	0	4·93	1·03	155·3	10·1	7		Hypochlorhydria.
							15	7·54	1·86	145·1			V.F.	
		,, ,,	I.M.	20 µg.	5	100 µg.	15	10·44	2·84	116·1			V.G.	
							40	10·73	3·14	108·2				
		,, ,,	I.M.	40 µg.	5	200 µg.	10	10·73	2·97	115·4			Nil	Left hospital

TABLE I.—*Details of Haematological Response at Days Indicated—(continued)*

Case No.	Age and Sex	Haematinic	Route	Dose			Day* of Treatment	Hb (g./%)	R.B.C. (mil./c.mm.)	M.C.V. (m.3)	Retics.		I.R.†	Remarks
				Daily	No. of Days	Total					%	Day		
11	20 M	Vit. B_{12}	I.M.	20 μg.	5	100 μg.	0	2·61	0·65	123·0	7·8	7		Hypochlorhydria. Blood picture reached normal level without further treatment
							15	2·90	0·67	164·1			Nil	
		Folic acid	Oral	30 mg.	30	900 mg.	15	6·38	1·87	128·3	7·6	5	G.	
							25	8·70	2·66	109·0				
							30	8·41	2·61	106·8				
		Vit. B_{12}	Oral	15 μg.	6	90 μg.	15	10·73	3·34	95·8			V.G.	
							25	12·32	3·67	98·0				
12	47 F	Vit. B_{12}	I.M.	40 μg.	3	120 μg.	0	7·54	1·68	136·7	2·8	7		Isochlorhydria.
							15	8·70	2·56	117·1			G.	
		,, ,,	I.M.	40 μg.	3	120 μg.	10	8·12	1·98	131·0			Nil	
		Folic acid	Oral	30 mg.	21	630 mg.	15	10·15	2·71	121·7			V.F.	
							20	11·02	2·87	118·4				
		Liver ext.	I.M.	3 ml.	6	18 ml.	10	11·02	2·88	121·5			Nil	Left hospital
13	43 F	Vit. B_{12}	I.M.	40 μg.	3	120 μg.	0	4·06	0·87	172·4	8·3	3		Isochlorhydria.
							20	6·49	2·73	120·8			G.	
							30	10·40	3·12	115·3				
							40	9·86	2·93	109·2				
		,, ,,	I.M.	40 μg.	3	120 μg.	10	10·73	3·26	98·1			G.	
							20	11·02	3·12	105·7				
		Folic acid	Oral	30 mg.	7	210 mg.	7	10·44	3·26	101·2			Nil	
		Liver ext.	I.M.	3 ml.	6	18 ml.	10	12·90	3·60	102·7			G.	
							30	13·05	3·70	97·2				Left hospital
14	27 F	Vit. B_{12}	I.M.	20 μg.	7	140 μg.	0	5·22	1·06	132·1	12·0	4		Hypochlorhydria.
							15	8·41	2·20	127·2			G.	
							25	8·12	2·23	130·0				
		Liver ext.	I.M.	3 ml.	6	18 ml.	15	8·99	2·50	120·0			Tol.	
		Vit. B_{12}	I.M.	15 μg.	10	150 μg.	17	9·86	2·74	109·4			Tol.	
							21	9·86	2·80	105·3				
		Folic acid	Oral	30 mg.	30	900 mg.	15	11·02	3·47	95·1			V.G.	
							30	11·31	3·36	103·9				Left hospital
15	25 F	Vit. B_{12}	I.M.	40 μg.	5	200 μg.	0	7·83	1·98	141·4	4·5	4		Isochlorhydria.
							15	8·40	2·31	138·6			F.	
		,, ,,	I.M.	40 μg.	5	200 μg.	15	8·70	2·97	104·3			G.	
		,, ,,	I.M.	40 μg.	5	200 μg.	10	8·84	2·84	112·6			Nil	
		Folic acid	Oral	30 mg.	15	450 mg.	15	8·99	3·49	91·6			V.G.	
							20	8·99	3·24	98·7				
		Liver ext.	I.M.	3 ml.	6	18 ml.	15	9·57	3·58	94·9			V.F.	Left hospital
16	40 M	Vit. B_{12}	Oral	10 μg.	4	40 μg.	0	10·44	2·64	121·2	3·5	3		Hyperchlorhydria. Left hospital, but further improvement without any other treatment
							15	11·6	3·21	115·2			V.F.	
		,, ,,	Oral	10 μg.	4	40 μg.	15	12·18	3·51	99·7			V.F.	
17	42 F	Vit. B_{12}	Oral	15 μg.	3	45 μg.	0	9·86	2·4	133·3	Nil			Isochlorhydria.
							15	10·15	2·72	113·9			F.	
		,, ,,	Oral	15 μg.	3	45 μg.	15	9·28	2·80	103·5			Nil	
							20		2·66					
		,, ,,	I.M.	15 μg.	5	75 μg.	15	10·44	2·98	110·8			F.	Left hospital
18	18 M	Vit. B_{12}	I.M.	20 μg.	6	120 μg.	0	4·35	1·14	131·5	15·2	7		Absolute achlorhydria at beginning, but isochlorhydria at end of treatment. Left hospital, further improvement without other treatment
							15	5·80	1·52	144·7			F.	
							25	8·41	2·29	131·0				
							40	10·67	2·85	112·2				
							50	8·70	2·76	106·0				
		Folic acid	Oral	30 mg.	15	450 mg.	7	9·86	2·87	104·0				
							15	9·86	2·76	111·0			Nil	
		Liver ext.	I.M.	3 ml.	6	18 ml.	7	11·02	3·86	82·5			V.G.	
19	45 M	Vit. B_{12}	I.M.	20 μg.	6	120 μg.	0	3·19	0·75	160·0	18	10		Hypochlorhydria.
							16	6·52	1·55	135·6			F.	
							25	6·81	1·85	120·0				
							32	6·67	1·85	122·0				
		Folic acid	Oral	30 mg.	15	450 mg.	7	9·28	2·18	131·0				
							15	9·28	2·35	120·5			F.	
		Liver ext.	I.M.	4 ml.	6	24 ml.	15	10·44	2·87	111·4			V.F.	Further improvement with more liver extract
							25	11·02	3·45	101·4				
20	25 M	Vit. B_{12}	I.M.	20 μg.	6	120 μg.	0	2·90	0·76	131·5	Nil			Hyperchlorhydria. Further improvement without other treatment
							15	4·49	1·38	123·3			F.	
							25	4·64	1·26	119·0				
		Folic acid	Oral	30 mg.	30	900 mg.	15	7·54	2·15	130·2			V.F.	
							30	8·70	2·97	101·0				
21	25 M	Vit. B_{12}	Oral	15 μg.	5	75 μg.	0	2·90	0·73	147·9	4·5	7		Hypochlorhydria. Improvement continued
							15	2·46	0·52	171·4			Nil	
		,, ,,	I.M.	15 μg.	5	75 μg.	15	2·32	0·82	146·3	3·1	6	Tol.	
		Folic acid	Oral	30 mg.	30	900 mg.	15	4·35	1·28	148·4			F.	
							50	10·44	3·47	100·8				
22	40 F	Vit. B_{12}	I.M.	40 μg.	3	120 μg.	0	5·80	1·77	107·3	Nil			Achlorhydria. Blood picture shows evidence of hypochromicity. Left hospital
							7	5·51	1·68	101·1			Nil	
		Folic acid	Oral	30 mg.	15	450 mg.	15	6·38	2·54	94·4			G.	

* 0 marks the beginning of the period of observation. † Improvement rate calculated according to the formula of Della Vida and Dyke: V.G.=Very good; G.=good; V.F.=very fair; F.=fair; Tol.=tolerable.

TABLE II.—*Result of Parenteral Vitamin B_{12} Treatment*

Improvement Index	No. of Cases	Improvement Sustained		Improvement Not Sustained	
		No.	Case Nos., with Dosage*	No.	Case Nos., with Dosage
Very good..	10	4	1 (70), 3 (150), 8 (250), 9 (250)	6	2 (120), 4 (300), 5 (240), 6 (340), 7 (240), 10 (500)
Good ..	4	0		4	12 (120), 13 (240), 14 (140), 15 (400)
Fair ..	4	0		4	17 (75), 18 (120), 19 (120), 20 (120)
Tolerable ..	1	0		1	21 (75)
Nil	2	0		2	11 (100), 22 (120)

*The amount of vitamin B_{12} (in μg.) required to produce the response is shown in parentheses after the case number.

TABLE III.—*Correlation of Improvement Index With the Dose of Vitamin B_{12} Given Parenterally*

Dose	Very Good	Good	Fair	Tolerable	Nil
Less than 100 μg.	1 (*1*)	0	1 (17)	1 (21)	0
100 to 200 μg. ..	2 (*2, 3*)	2 (12, 14)	3 (18, 19, 20)	0	2 (11, 22)
200 to 300 μg. ..	4 (*5, 7, 8, 9*)	1 (13)	0	0	0
300 to 500 μg. ..	3 (*4, 6, 10*)	1 (15)	0	0	0
Total ..	10	4	4	1	2

Case numbers are given in parentheses. Cases showing sustained improvement are in italics.

sustained improvement in two cases (Nos. 8 and 9), but did not produce further improvement in three others (Nos. 10, 12, and 14).

Vitamin B_{12} Orally

Seven cases (Nos. 3, 8, 9, 11, 16, 17, and 21) had vitamin B_{12} orally. Apart from Case 11 this treatment was given first. The dose was usually small, less than 100 μg., but Cases 8 and 9 each had 500 μg. Of the six cases that were given oral vitamin B_{12} initially, one (Case 16) showed very fair and sustained improvement with 40 μg., and another (Case 17) showed fair improvement, which was not sustained, with 45 μg. No appreciable improvement was noted in the other four cases, though two of them (Nos. 8 and 9) had large doses. Cases 3, 8, and 17 had normal gastric acidity, Cases 9 and 21 had hypochlorhydria, and Case 16 had hyperchlorhydria. Thus no correlation of the improvement rate was found either with the dose of vitamin B_{12} given orally or with the state of gastric acidity.

The seventh case (No. 11), with hypochlorhydria, showed very good improvement with 90 μg. of vitamin B_{12} orally, and the improvement was sustained. Prior to this treatment the patient had shown good improvement with folic acid, which, however, was not sustained. Before the folic acid he had had vitamin B_{12} parenterally without any appreciable improvement.

Oral and Parenteral Vitamin B_{12} in Same Patient

Six of the seven cases treated with oral vitamin B_{12} were also given vitamin B_{12} parenterally—five after and one before the oral treatment. Of the four cases which did not improve with oral treatment, three (Nos. 3, 8, and 9) showed very good improvement after parenteral treatment, and the improvement was sustained in all of them. In Case 17 the response was about equal with oral and parenteral therapy. Case 11 did not show any response with parenteral treatment, but a very good response with oral treatment, and the improvement was sustained. As mentioned already, this case showed good improvement with folic acid prior to oral treatment. Thus generally a better response was seen with parenteral treatment.

Response to Other Haematinics

Cases showing suboptimal response with vitamin B_{12} were first given folic acid (14 cases) and those still failing to reach normal level were given liver extract parenterally (eight cases). The improvement index is shown in Table IV.

TABLE IV.—*Response to Folic Acid and Liver Extract in Cases Not Showing Sustained Improvement With Vitamin B_{12}*

Haematinic	Total No.	Improvement Index			
		Very Good and Good	Very Fair and Fair	Tolerable	Nil
Folic acid ..	14	8 (2, 4, 5, 6, 11, 14, 15, 22)	4 (12, 19, 20, 21)		2 (13, 18)
Liver extract ..	8	4 (2, 5, 13, 18)	2 (15, 19)	1 (14)	1 (12)

The case numbers are given in parentheses.

Compared with parenteral vitamin B_{12}, folic acid produced greater improvement in six cases (Nos. 11, 14, 15, 20, 21, and 22), equal response in four (Nos. 2, 4, 5, and 19), and less response in four (Nos. 6, 12, 13, and 18). The difference was well marked in four cases—in two (Nos. 11 and 22) there was no improvement with vitamin B_{12}, but good improvement with folic acid, while the other two (Nos. 13 and 18) showed good and fair improvement with vitamin B_{12}, but no improvement with folic acid.

Compared with vitamin B_{12} and folic acid, liver extract produced definitely better response in one case (No. 18), about equal response in three cases (Nos. 2, 5, and 19), and less response in three cases (Nos. 12, 14, and 15). One case (No. 13) showed about the same response as with vitamin B_{12}, but a better response than with folic acid. The difference in response was well marked in three cases, being in favour of liver extract in Case 18, and in favour of vitamin B_{12} and folic acid in Cases 12 and 14.

Reticulocytosis.—Adequate reticulocyte response was not seen in any of the cases after vitamin B_{12} orally or parenterally, even when the improvement in the red-cell count was very good (Table I).

Macrocytosis.—In all except two cases (Nos. 1 and 11) macrocytosis persisted for a considerable period after vitamin B_{12} therapy, when the increase in the red-cell count was found to be very good, including those cases in which the blood reached normal levels without any further treatment.

Discussion

Published reports on the effect of vitamin B_{12} in N.M.A. are still too scanty to permit any definite conclusion to be drawn. Patel (1948), Spies *et al.* (1949), and Chaudhuri (1951) have reported favourably on the effect of vitamin B_{12}. On the other hand, contrary views have been expressed by Luhby (1949), Bethell (1950), and Davidson and Innes (1951). Our earlier impression had been that vitamin B_{12} produces a suboptimal response in N.M.A. (Das Gupta, 1951, Das Gupta and Chatterjea, 1951).

In the present series initially good improvement was noted in 14 out of the 22 cases (64%), but the improvement was sustained and reached the normal level with vitamin B_{12} alone in only five cases (23%). Reticulocytosis after vitamin B_{12} was poor in all cases, and there was no correlation between the improvement index and the reticulocyte response. After vitamin B_{12} macrocytosis was found to persist for a long time in most of the cases which showed very good improvement. Folic acid was given after vitamin B_{12} in 14 cases, with good response in eight of them, but the blood picture reached a normal level in only four. Still later, crude liver extract was given to eight cases which had failed to reach a normal level after vitamin B_{12} and folic acid, and all except one showed further response, the blood picture reaching a normal level in three of them.

In general the response to vitamin B_{12} had no distinct correlation with the dose of vitamin B_{12}, with the route of administration, or with the state of gastric acidity, but the maximum response was usually obtained with 200 to 300 μg. of vitamin B_{12}, given intramuscularly. Great variation in response to vitamin B_{12} was noted not only among the different cases but also in the same case at different times. In some cases large doses of vitamin B_{12} failed to produce

any further improvement after good initial improvement had been obtained with smaller doses. All these cases, however, showed further improvement with folic acid.

The present study indicates that both folic acid and vitamin B_{12} are valuable agents in the treatment of N.M.A., and we are inclined to think that N.M.A. represents deficiency of both folic acid and vitamin B_{12}. Deficiency of folic acid is probably the major and primary factor, as is evident from the good response obtained with folic acid in cases of N.M.A. (Das Gupta and Chatterjea, 1946), and of macrocytic anaemia in pregnancy (Das Gupta and Chatterjea, 1949), and deficiency of vitamin B_{12} the minor and secondary factor.

In an average case of N.M.A., administration of vitamin B_{12} will correct only the B_{12} deficiency and produce a response which might appear to be optimum initially. During the period of B_{12} activity some amount of available folic acid will be used up, producing further deficiency of folic acid in the system. In this way extreme deficiency of folic acid may result, and at this stage no further improvement is possible with vitamin B_{12}. Obviously folic acid in this situation will in the majority of cases bring the blood picture to normal. The complete success of vitamin B_{12} in an occasional case may be explained by assuming that a considerable amount of folic acid is available in such a case for utilization by B_{12}.

Failure of oral vitamin B_{12} therapy even with massive dosage, and subsequent improvement with smaller dosage of the vitamin given parenterally, proves that absorption of B_{12} must be severely impaired in N.M.A. In N.M.A. the degree of this malabsorption may not run parallel with the gastric acidity, and may in fact be quite independent of gastric hydrochloric acid. It is probable that in N.M.A. the absorption of vitamin B_{12} is determined by the condition of intestinal absorptive surface. We have observed a temporary and reversible type of histamine-fast achlorhydria in N.M.A. In these cases (No. 18 of the present series is an example), along with the improvement of anaemia there is a return of hydrochloric acid. It is possible that a few of these cases may also have a temporary phase of diminished intrinsic factor activity.

In the majority of cases of N.M.A. folic acid alone would be sufficient, because vitamin B_{12} deficiency is a minor one and never extreme. As the requirement of vitamin B_{12} is very small this is easily obtainable from the diet, especially after administration of folic acid, which would improve the absorption of B_{12} from the gastro-intestinal tract. This will explain the success we obtained with folic acid in cases of N.M.A. and the macrocytic anaemia of pregnancy.

It should, however, be emphasized that N.M.A. cases in different parts of the world may vary in their degree of deficiency of vitamin B_{12} and folic acid, depending on the dietary habits and gastro-intestinal condition. The response to vitamin B_{12} and/or folic acid depends both on absolute and on relative deficiency of the two factors, which may explain the difference in response obtained by workers in different places.

The superiority of crude liver extract over folic acid and vitamin B_{12} in some cases of N.M.A. may be explained by its complex character, its content of vitamin B_{12}, folic acid, folinic acid, and other members of the vitamin-B complex possibly having a synergistic effect, ensuring optimum haemopoiesis. Whether or not liver extract contains any other still unidentified factor—for example, accessory factors of Jacobson and Subbarow (1937) or protein synthesis factor of Owren (1951)—which may be valuable in the treatment of N.M.A., cannot be stated with certainty in the present state of our knowledge.

Summary

The results of treatment with vitamin B_{12} administered intramuscularly in 21 cases and orally in seven cases of nutritional macrocytic anaemia are reported.

Though the initial improvement index was good in 64% of cases, sustained remission was obtained in only 23%. Reticulocytosis after vitamin B_{12} therapy was inadequate, and there was no correlation between the improvement index and the reticulocyte response. Macrocytosis tended to persist even in cases showing very good improvement. Folic acid and crude liver extract evoked adequate or better response in most cases not showing sustained remission with vitamin B_{12}.

In general, maximum response was obtained with 200–300 μg. of vitamin B_{12} given intramuscularly, but this response had no distinct correlation with the dose. The response to oral vitamin B_{12} also had no correlation either with the dose or with the state of gastric acidity.

The present studies definitely indicate that N.M.A. represents deficiency of both folic acid and vitamin B_{12}, deficiency of folic acid being the major and primary factor, and that of vitamin B_{12} the minor and secondary factor in most cases.

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In his last annual report on the health of Edinburgh (*Annual Report of the Public Health Department for the Year 1952*) Dr. W. G. Clark, who has recently retired from the post of medical officer of health, has included a chapter on tuberculosis. After reminding us that it was in Edinburgh that the tuberculosis dispensary system was first conceived—a development which was to have a profound effect on tuberculosis practice throughout the world—Dr. Clark examines the recent trend of the disease in the city. While the death rate fell from 60 deaths per 100,000 of the population immediately before the war and 62 in 1948 to 26 in 1952, the notified incidence of the disease rose steadily; in 1939 there were 92 notifications per 100,000, in 1952 there were 154. These increases are reflected in the number of cases of pulmonary tuberculosis on the Tuberculosis Register; in 1938 their number was 1,769, by 1952 it was 3,524. The easy explanation for the rise is that it was due to improved case-finding as a result of the widespread adoption of mass miniature radiography. However, this view was strongly challenged by the Tuberculosis Committee of the Scottish Health Services Council in 1951. Now Dr. Clark, on the basis of more up-to-date information, is able to show that at least a sizable proportion of the increase in notifications was due to earlier case-finding. He adds: "It would be unwise, however, to accept this as a complete answer."

THE NATURE AND TREATMENT OF PLUMMER-VINSON DYSPHAGIA

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This syndrome of dysphagia of upper oesophageal type associated with present or past anaemia is relatively common in the North of Ireland. Treatment by dilatation is very satisfactory, but the condition is unfortunately often misdiagnosed as hysteria or "nervous swallow." Indeed, Vinson in 1922 put forward the view that the dysphagia was hysterical. We have been impressed by the diagnostic difficulty the condition evidently offers and by the consequent prolonged physical and social distress the patient suffers. That the condition is due to an organic stricture and that relief may be obtained by dilatation have been pointed out by McGibbon (1935), but these observations have not become widely known. This account is based on 16 cases observed in the last five years. Details of these cases are given in the Table.

Clinical Features

The clinical features have often been described, among others by McKenzie (1918), Brown Kelly (1919, 1927), Paterson (1919), and Munro Cameron (1928, 1929). The onset is insidious and the course lasts many years. There is no tendency to spontaneous cure. The social class and the level of intelligence are below average. Their lack of understanding often makes it difficult to persuade these patients to be treated (19% of our patients offered dilatation refused). The condition occurs only in women, and usually begins in the child-bearing years. There always is or has been in the past an iron-deficiency anaemia of long standing; and associated with this in varying degree are the usual features of smooth tongue, splenomegaly, spoon-nails, and angular stomatitis. Very acute orificial stomatitis is not common. The pallor often has a yellowish tinge, and is due as much to change in skin pigmentation as to low haemoglobin. Courses of iron produce no permanent improvement in the anaemia if not repeated twice a year. If the patient has been treated energetically with iron the anaemia may be mild and there may be no glossitis or stomatitis.

Some cases may be seen after the menopause, when improvement in the anaemia has occurred and only the dysphagia remains. The E.S.R. is sometimes inexplicably high (Cases 2, 5, and 6). Emaciation is rare, though some patients put on considerable weight after dilatation. Since all usual foods except meat can be reduced to a pulp by cooking processes or by chewing, these patients can usually take enough calories. It is almost invariable that these people have not been able to eat meat for years and that their diet shows a selective meat deficiency.

Morbid Anatomy and Oesophagoscopic Appearances

The dysphagia is due to organic stenosis in the upper oesophagus at or just distal to the introitus of the oesophagus. The site of the obstruction is either at the level of the crico-pharyngeal sphincter or immediately beyond it. When it is at the level of the sphincter the mouth of the oesophagus does not open in front of the advancing oesophagoscope enough to allow it to pass, the lumen at the level of stricture being sometimes only a few millimetres in diameter. Sometimes the lumen appears in the middle of a diaphragm-like obstruction. Often some degree of stenosis extends for

Details of Cases

Case	Age	Haemoglobin %	E.S.R.	Spleen	Oesophagus		Duration of Dysphagia	Menses	Cancer	Stricture Dilated	Result	Remarks
					Endoscopy	*X*-ray						
1	40	100	—	+	Tight introital stricture	Cuffing and web	20 years	Hysterectomy at 38	Nil	+	Good	Mother said to have died of pernicious anaemia. Sister said to have P.A.
2	56	100	34	—	Introital stricture and web	Cuffing and two webs	6 ,,	Ceased	,,	+	,,	Fat absorption normal. Needs dilating yearly
3	60	58	10	+	Web	Web	Many ,,	,,	,,	+	,,	Gastro-enterostomy years ago
4	37	87	0	+	Stricture at 15 cm. from upper teeth	Unsatisfactory because of choking	10 ,,	No information	Squamous epithelioma 1 year after dilatation	+	Died	Benign stricture at first examination. 1 year later cauliflower carcinoma as well
5	64	100	24	+	Refused	,, ,,	Many ,,	Ceased	Nil	Refused	No change	Lives on semi-fluids
6	46	64	20	—	Diaphragm	Web	5 ,,	Regular	,,	+	Good	Hypertension. Haemoglobin remains low
7	65	74	—	—	Introital stricture	,,	"Always"	Ceased	,,	+	,,	
8	49	95	10	—	Introital stricture. Squamous carcinoma at 22 cm.	Carcinoma	Uncertain	,,	+	+	Died	Clinical typical Plummer-Vinson disease. Exacerbation of dysphagia and *x*-ray diagnosis of carcinoma
9	77	86	2	—	Refused	No study	,,	,,	Nil	Refused	No change	Grossly deficient diet. Stated to have P.A.; on vitamin B_{12}. Acute orificial stomatitis
10	48	56	17	—	Web	,, ,,	8 years	Regular	,,	+	Good	Haemoglobin remains low
11	41	70	7	+	Introital stenosis	Web	1 year	,,	,,	+	,,	Has also a papilloma of a vocal cord
12	48	60	8	—	Refused	No study	9 months	,,	,,	Refused	No change	Always bloodless
13	65	Normal	—	—	Not offered	Web	Years	Nil	,,	Not offered. Can eat meat with care	,, ,,	Anxiety state. Atheromatous vascular disease
14	58	75	—	—	,, ,,	,,	,,	,,	,,	,, ,,	,, ,,	Angina of effort. Gastro-enterostomy in 1914. Severe iron-deficiency anaemia from 1932. Glossitis ++. Occult blood test negative
15	73	46	13	+	,, ,,	No study	,,	Uterine bleeding	,,	Not offered	,, ,,	Bleeding uterine fibroid for many years. Hysterectomy. Pathological diagnosis carcinoma of body of uterus
16	42	49	17	—	Awaiting dilatation	,, ,,	2 years	Regular. Heavy	,,	Awaiting	,, ,,	Active mucosal changes in mouth and on lips. Chokes on meat and bacon

a varying distance, up to a centimetre or so, along the oesophagus. In a few cases one is able to introduce the oesophagoscope through the sphincter and then almost immediately beyond this is seen a web of mucosa, occluding perhaps two-thirds of the lumen and ending in a free crescentic edge. There may be two webs (Case 2). However, it is our impression from endoscopic examination that web formation is less often the cause of the obstruction than would appear from *x*-ray examination. We think that the *x*-ray appearance of a web may often be due to viewing from the lateral aspect a diaphragm-like obstruction with an eccentric opening in it. No oesophagitis or areas of ulceration have been seen in these cases.

It is emphasized again that there is an anatomical narrowing to cause the dysphagia. There is no muscular spasm or achalasia. It should be noted that a narrowing which lower in the oesophagus would be asymptomatic will at the introitus cause severe dysphagia.

The Dysphagia

Because of the site of the narrowing at or just beyond the introitus the dysphagic difficulty consists in the patient not being able to move food from the hypopharynx into the oesophagus. It is this feature that differentiates this dysphagia from lower oesophageal dysphagia. The bolus mills about in the hypopharynx on the very verge of the glottis. The patient, anxious, even desperate, makes repeated and ineffective attempts to swallow—ineffective because to make an effective attempt would drive the food into the larynx. The sensation of being about to choke, of something about to go the wrong way, is instant. Drinking something to help is impossible—and useless. Eventually the patient, unable to swallow and about to choke, with much unpleasant hawking and spitting, brings up the food mouthful. This spitting out at the table is as characteristic of Plummer–Vinson dysphagia as vomiting or the emptying of a full oesophagus *after* a meal is typical of a low oesophageal obstruction. Note that in Plummer–Vinson disease there is no accumulation or retention of food or fluid. The anxiety, the violent hawking up, the complaint of choking, the unwillingness of the patient to swallow effectively enough to satisfy the onlookers, lend themselves to a diagnosis of hysteria—as readily made by the physician as by the family. Further features of the dysphagia are the slowness of eating, and the occasional completion of the obstruction—for example, by a pea (Case 6). This is not a painful dysphagia, unless carcinoma has supervened.

There should be little difficulty in distinguishing this disease on clinical grounds from neurological, hysterical, or anxiety dysphagia. Endoscopy clinches the diagnosis. A negative barium swallow is valueless in excluding it.

Complications

The most important complication is the onset of carcinoma, usually in the upper oesophagus but sometimes in the lower oesophagus or in the stomach. The syndrome is the precursor of post-cricoid carcinoma (Simpson, 1939), and the prophylaxis of the syndrome should prevent these cancers occurring. The onset of carcinoma is marked by hoarseness, painful swallowing, and increasing obstruction. Inability to swallow saliva may be the first sign of cancerous change.

Rejection by the family may be serious. Sometimes (Cases 1 and 10) the patient has eaten for years in a separate corner because her family could not bear to have her at the table with them. In Case 1 there was marital estrangement and delinquency in the children.

Lung complications are rare. Case 2 had a lung collapse some years before diagnosis, presumably due to spill-over.

Management

The basic and only essential requirement in treatment of this dysphagia is dilatation of the stenosis. This is easily and satisfactorily accomplished. It can be done, if necessary, with only local analgesia and without admission to the ward. It should be done under direct vision through an oesophagoscope and not by blind dilatation, both because this would be difficult to carry out in cases of stricture at the entrance to the oesophagus and because it is advisable to exclude the presence of a carcinoma. Hurst's mercury bougies are unsuitable.

Before the oesophagoscope can be passed through the stenosed area the stricture almost always has to be dilated with gum-elastic bougies, beginning with one of the smaller sizes and working up to as large a size as can be passed down the instrument. It is then possible to use the oesophagoscope itself as a dilator by passing it through the stricture. The rest of the oesophagus is then examined to exclude carcinoma lower down. An oesophagoscope 4.6 cm. in circumference has been used in this condition. It would in most cases be difficult and probably dangerous to attempt to dilate the stricture enough to allow a large instrument to pass.

The role of radiology is to exclude cancer lower down and in the stomach. Demonstration of the stenosis is possible with special care, but will often be missed at a routine barium swallow. There are some important points in visualizing the stricture with the *x*-ray screen. Barium suspensions of creamy consistency are used. For obvious reasons, thick barium cannot be used in these patients, and thin barium passes too rapidly for visualization. The patient should be turned into the left oblique position till the air-filled pharynx and trachea and the retrotracheal space clear the spine. The observer must fix his gaze on the upper inch (2.5 cm.) of the oesophagus. This is roughly 1½ in. (3.8 cm.) below the point where the pharynx ceases to be air-containing—that is, below the entrance to the larynx. If the patient then swallows a mouthful of barium the abnormality will easily be seen for as long as three to four seconds, but no more. Most cases show a general narrowing at the beginning of the oesophagus which is pronounced enough in some

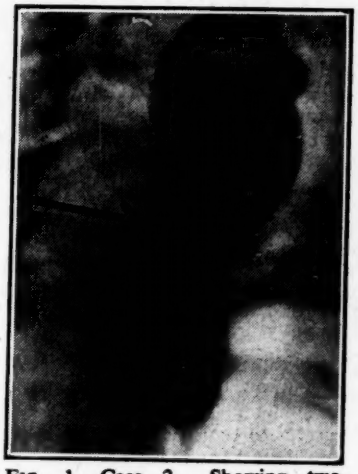

FIG. 1.—Case 2. Showing two "webs" at either end of a cuff-like stenosis about 1 cm. in length, and hypopharyngeal bulging above the obstruction.

FIG. 2.—Case 1. Showing a web appearance anteriorly at the level of the crico-pharyngeal bulge, which is well seen posteriorly. The "web" is at the level of the fifth cervical vertebral body.

FIG. 3.—Case 1. Showing web appearance particularly well.

severe cases to produce a cuff-like appearance (Fig. 1). In addition most cases when viewed laterally show the well-known web appearance (Figs. 2 and 3).

For reasons of safety, gastroscopy is not undertaken, though the condition of the gastric mucosa is of great theoretical interest. Gastroscopists should beware of women in this age group, since they may have an undeclared stenosis of this kind.

Follow-up should be directed to securing a permanently normal haemoglobin, and redilatation should the stenosis recur. In the worst cases a surgical or radium menopause may be necessary if oral iron cannot keep the blood normal. Frequent endoscopy to detect early cancerous change is impractical and of doubtful value.

If the anaemia is gross it should be corrected before dilatation. However, no quantity of iron will correct the dysphagia. If in doubt whether to dilate or not it is useful to remember that inability to eat meat is an absolute indication for the procedure.

Prognosis and Causation

Redilatation may be needed as often as every year (Case 2). Repeated courses of iron will be necessary till the menopause occurs. Two of our 16 cases developed carcinoma (Cases 4 and 8). Simpson (1939) reported that 10 of his 18 cases developed carcinoma.

The cause of mucosal atrophy in the upper gastro-intestinal tract, the relationship of this to hypochromic anaemia, and the relationship of both to the oesophageal stenosis are quite unknown. Whatever the condition of the gastro-intestinal tract, it seems clear that the dysphagia does not occur unless iron-deficiency anaemia has been present. Despite superficial resemblances there seems to be no relationship to ariboflavinosis. The exclusive incidence in women is sufficiently accounted for by their peculiar liability to menstrual blood-loss anaemia. The incidence of hypochromic anaemia in Northern Ireland is considerable, and is to be attributed to the inadequate nutrition common in middle-aged women in Northern Ireland and to uncorrected menorrhagia. The implications for prophylaxis of post-cricoid carcinoma by improved nutrition and effective treatment of menorrhagia are obvious.

Summary

The clinical diagnosis of Plummer–Vinson disease is described. The dysphagia is due to organic stenosis. Dilatation of the stricture is the essential treatment. Plummer–Vinson disease is a pre-cancerous condition.

We are much indebted to Mr. Kennedy Hunter, Mr. R. S. McCrea, Mr. W. Matthews, and Dr. Martin Beare for the opportunity of studying their patients, and to Mr. D. Mehaffey, A.R.P.S., for the photographs.

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A guide to epileptic colonies, the accommodation they offer, their charges, training, etc., has been published by the British Epilepsy Association (price 1s.). Although only sane epileptics are admitted to the colonies, the standards of subnormality for exclusion vary. The handbook gives details for each colony of the method of admission and administration, conditions for discharge of patients, and the length of the waiting-list. The booklet points out that, while the provision of a permanent sheltered home remains an important function of these colonies, the main object of care is to stabilize the patient sufficiently to permit return to work.

ANTI-SIALOGOGUE AND OTHER EFFECTS OF ATROPINE MUCATE

BY

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Although it is barely 50 years since atropine began to be used to inhibit salivary secretion before the administration of an anaesthetic, this drug has come to be regarded as an essential requirement in these circumstances. Pre-operative administration of atropine is so important that if it has been omitted most anaesthetists would either postpone the operation or administer atropine intravenously.

In big hospitals with long operating lists it is usually impossible to estimate the correct time for the administration of atropine. Any preparation of this drug whose effect would be so prolonged that accurate timing was unnecessary would be an important and welcome innovation. We regarded it as of some clinical importance, therefore, to investigate further the claim made by Asquith and Thomas (1948) that hypodermic injections of atropine mucate ("hyperduric atropine") lead to a more prolonged inhibition of salivary and mucus secretion than do the more commonly used atropine sulphate or tartrate.

Asquith and Thomas in their paper relied on clinical observation and apparently used no criterion for assessing the anti-sialogogue effect, other than their own or their patients' opinion. We decided to use a more objective and quantitative method of estimation, in volunteers in whom many environmental factors could be controlled.

The only published method we found for studying salivary secretion was that of Lashley (1916), and its modification by Richter and Wada (1923). In this method the parotid duct is cannulated and the saliva allowed to flow through a long glass tube. The passage of a bubble of air introduced into the stream of saliva is timed over a measured distance. This method was deemed unsuitable for an experiment requiring frequent observations over a period of perhaps six hours. We considered and discarded the suitability of other methods of cannulation of one or more salivary ducts. Electrical measurement of the wetness of the mucosa of the mouth was unsatisfactory, and so was weighing pledgets of wool allowed to soak saliva for a fixed time.

Method

We finally devised the following method for measuring the salivary activity at any particular moment. The subject swallows repeatedly, to get rid of any saliva present in the mouth. Four drops of lemon juice (a powerful if not a specific stimulus) are then placed on the tongue and allowed to act for 30 seconds. The mouth is then rinsed for 15 seconds with 5 ml. of water, the subject then spitting into a funnel and measuring cylinder. For a further 15 seconds the mouth is emptied by repeatedly spitting into the measur-

ing cylinder. The froth on the collected washings is touched with a glass rod dipped in caprylic alcohol, and the rinsings are measured. This amount minus 5 ml. is the salivary secretion in response to the lemon-juice stimulus. We call this amount the salivary index.

The salivary index was first measured at quarter-hour intervals for about one hour before injection was made. A dose of 1/100 gr. (0.65 mg.) of either atropine mucate or atropine sulphate was then injected subcutaneously over the deltoid muscle in the arm and the index measured every 15–20 minutes until several consecutive readings had returned to the pre-injection range. The pulse was counted each time the salivary index was obtained. Each subject submitted to testing with atropine mucate on one day and to atropine sulphate on another day. Altogether nine subjects were tested, and a series of "paired" results were obtained.

Subjective Sensations.—All the subjects felt dry at the height of the action of the drugs. Beyond that point their opinion was unreliable, being often at variance with the salivary index. Several of them thought that salivary secretion was free when measurement showed that it was still very depressed. A few of the subjects felt drowsy when the action of both types of atropine was at its maximum. Two of them actually fell asleep for a short period. This is perhaps not surprising, since atropine, an "alkamine ester" (Dawes, 1946a, 1946b), has much in common with the members of this group, such as the antihistamines and the local anaesthetics. In the doses used, little subjective effect on the accommodation, gut, or heart rate was observed by the volunteers.

Objective Phenomena.—The subjects did not look flushed, and their pupil size was variable—several of them having dilated pupils, others being unaffected. Some of them looked obviously drowsy and heavy. All were able to read and write, accommodation being hardly affected.

Pulse

The average pre-injection pulse rate for each subject was taken as 100% and the post-injection rates were expressed in percentage form. The mean values of these percentages for all subjects combined at various intervals of time after the administration of the drugs were then calculated, and are presented diagrammatically in Fig. 1.

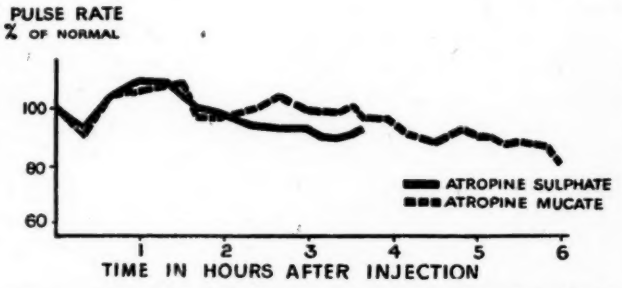

FIG. 1.—Mean pulse rate after injection of atropine sulphate and atropine mucate.

The pulse showed great variation throughout the experiments. With both the sulphate and the mucate there was an initial slowing, followed by a rise above the pre-injection level. The magnitude of this rise appeared to be similar with both salts. The pulse rate then gradually slowed, and was still declining in rate when the experiments ended many hours after the injection.

The final rates were well below the pre-injection level. We have no knowledge of whether the pulse would have returned to the "normal" level had the observations been continued long enough. We feel, however, that the "normal" pulse rates may in fact have been elevated owing to the natural excitement before such an investigation.

Saliva

Although there was but little difference between the average pre-injection saliva values of each subject on the two days occupied by the experiment (see Table I) these "normal" salivary indices varied considerably between the subjects.

TABLE I.—*Difference Between the Means of the Pre-injection Saliva Values*

Subject	Before Mucate	Before Sulphate	Difference (S–M)
L. M.	6·40	6·13	−0·27
J. C.	7·65	7·22	−0·43
D. D.	3·97	4·27	+0·30
A. H.	8·17	8·42	+0·25
R. L.	5·27	5·02	−0·25
D. C.	8·30	7·30	−1·00
S. G.	6·42	5·07	−1·35
K. H.	5·00	5·61	+0·61
W. W. M. ..	5·54	4·73	−0·81
			−2·95

Mean of the differences = $-0{\cdot}329 \pm 0{\cdot}216$; $t = 1{\cdot}53$; $t_{.05} = 2{\cdot}31$, therefore not significant.

Because of this the results were treated in a similar way to those of the pulse rates—the average pre-injection values being taken as 100% and the post-injection saliva values expressed in percentage form. The means of these percentages based on all subjects are presented diagrammatically in Fig. 2 for various intervals of time. From this diagram

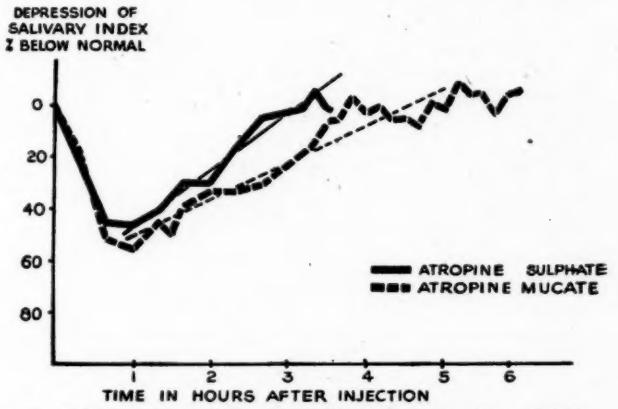

FIG. 2.—Mean saliva values after injection of atropine sulphate and atropine mucate.

it appears that, on the average, mucate of atropine reduces the salivary index 56%, and sulphate of atropine only 46%, of the pre-injection level: also that these minimum levels are reached with both drugs at one hour after injection. Consider, however (Table II), the individual minimum levels and the times at which they were reached.

The statistical test indicates that from these data we are unable to demonstrate any real difference between the mini-

TABLE II.—*Minimum Salivary Indices, and the Intervals after Injection at Which They were Attained*

Subject	Mucate		Sulphate		Difference in Minimum Levels (S–M)
	Minimum Level % of Normal	Time	Minimum Level % of Normal	Time	
		hrs. min.		hrs. min.	
L. M. ..	34·4	1 30	48·9	1 00	+14·5
J. C. ..	34·0	1 00	54·0	0 40	+20·0
D. D. ..	37·7	1 00 1 30	37·4	1 00 1 20	− 0·3
A. H. ..	59·9	0 40	62·9	0 40	+3·0
R. L. ..	30·4	1 20	11·9	0 40	−18·5
D. C. ..	45·8	0 40	47·9	0 20	+2·1
S. G. ..	28·0	1 00	35·5	1 40	+7·5
K. H. ..	52·0	1 00	60·5	1 00	+8·5
W. W. M. ..	52·3	0 40 1 00	61·3	1 00	+9·0

Mean difference = $5{\cdot}1 \pm 3{\cdot}62$; $t = 1{\cdot}41$; $t_{.05} = 2{\cdot}31$. Not significant.

mum levels of the salivary index attained by the two drugs. It can also be seen that the earliest time a minimum level was recorded with mucate was 40 minutes, and the latest time 1 hour 30 minutes. With sulphate the corresponding times were 20 minutes and 1 hour 40 minutes.

The minimum levels as recorded are not, however, strictly accurate. From the records of one subject, for example, we know that at 40 minutes his saliva level had been reduced to 44%, at 1 hour to 34%, and that at 1 hour 20 minutes it was back again at 52%. Whether it went below 34%, either between 40 minutes and 1 hour or between 1 hour and 1 hour 20 minutes, cannot be established. These considerations have still more force in other subjects—and in any further experiments the necessity of taking recordings more frequently during the period 40 minutes to 1 hour 30 minutes to establish the precise minimum is evident.

Return to Normal

Although there is not enough evidence to justify a conclusion that a lower level of secretion is reached with mucate of atropine the trend of the two curves (Fig. 2) suggests that with mucate a longer time is taken to return to the normal range than with sulphate. This is the next issue to examine.

As a first approach, the mean difference between the paired readings with mucate and sulphate was calculated at all points of time where nine paired readings were available—in the same manner as was done in Table II for paired minimum readings. The results are shown in Table III.

TABLE III.—*Mean Difference Between Paired Salivary Indices at Specified Intervals after Injection (Following Attainment of Lowest Level)*

Time after Injection	Mean Difference (S-M) ± S.E. (9 Subjects) % of Normal	t
1 hour	+9·6 ± 4·70	2·05
1 hour 20 min. ..	+3·9 ± 4·65	0·84
2 hours 20 min. ..	+17·3 ± 5·24	3·30*
3 hours	+20·4 ± 5·70	3·58†

* Significant at 5% level. † Significant at 1% level.

At every point of time, as is also evident from Fig. 2, the level of the mean salivary index was lower with mucate than with sulphate. At 1 hour after injection the difference amounted to 10% of normal, but was not significant. At 1 hour 20 minutes the difference was only 4%, but this alteration was not outside the range of random fluctuation. By 2 hours 20 minutes after injection the difference had reached 17%—significant at the 5% level—and at 3 hours it amounted to 20% of the pre-injection average—significant at the 1% level.

The increasing divergence of the two series indicated that the rate of return from lowest level to normal was slower after injection with mucate than with sulphate of atropine, and suggested that the fitting of suitable regression lines to each series of values, following the attainment of minimum level, would enable one to estimate the difference in time between the two drugs in returning to, say, 60%, 75%, etc., of normal. (It was not thought advisable to fit curves to the complete series—from injection to reattainment of normal range—because of the doubt about the precise value of the minimum points.)

Test of Deviation from Linear Regression

Statistical tests showed that during return to normal the relationship between the values of the salivary index and intervals of time after injection did not depart significantly from linearity. In other words, no significantly better fit would be obtained by using a curved rather than a straight regression line.

The essential data of the tests are given in Table IV. In the mucate series those values of the salivary index between 1 hour and 5 hours 20 minutes inclusive, and which were based on four or more subjects, were included. In the sulphate series *all* values of the index at 20-minute intervals between 1 hour and 3 hours 40 minutes were used.

TABLE IV.—*Analysis of Variance of Salivary Index at Different Times after Injection with Atropine Mucate During Return to Normal*

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Within time groups (error) ..	93	15,462·97	166
Between times	15	36,129·94	2,409
Total	108	51,592·91	
F = 2,409/166 = 14·5; $F_{\cdot 05}$ = 1·78			
Analysis of Sum of Squares for the Time Means			
Between times (above)	15	36,129·94	
Linear regression	1	33,840·82	
Deviations from linear regression	14	2,289·12	163·51
Error (from above)	93		166
F = 163·51/166 < 1·0; $F_{\cdot 05}$ = 1·8			

The upper section of the Table merely confirms that the mean values differed significantly at the various intervals, but it supplies the data necessary for the second half of the Table, from which we learn that the mean square corresponding to deviations from linear regression, far from being significantly greater than that for error, is, in fact, less. This indicates that nothing more than random sampling departure from linearity is present. The same conclusion is reached from Table V regarding the atropine sulphate series.

TABLE V.—*Analysis of Variance of Salivary Index at Different Times after Injection with Atropine Sulphate During Return to Normal*

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Within time groups (error) ..	58	14,374	248
Between times	8	18,041	2,255
Total	66	32,415	
F = 2,255/248 = 9·10; $F_{\cdot 05}$ = 2·11			
Analysis of Sum of Squares for the Time Means			
Between times (above)	8	18,041	
Linear regression	1	17,280	
Deviation from linear regression	7	761	109
Error (from above)	58		248
F = 109/248 < 1·0; $F_{\cdot 05}$ = 2·17			

Regression of Salivary Index (*y*) on Hours after Injection (*x*)

The equations to the regression lines (shown in Fig. 2) were found to be:

Mucate : $y = 13.95x + 35.0$ ... ... **A**

Sulphate : $y = 22.01x + 31.38$ ... ... **B**

where x is the number of hours after injection and y is the salivary index expressed as a percentage of the average pre-injection readings. These gave the values of salivary index at hourly intervals after injection, which are presented in Table VI.

From this we see that at one hour after injection—which has already been provisionally accepted as the time at which

TABLE VI.—*Values of Salivary Index at Hourly Intervals after Injection—as Calculated from the Regression Equations*

Hour after Injection (*x*)	Salivary Index (*y*)	
	Mucate % of Normal	Sulphate % of Normal
1	49·0	53·4
2	62·9	75·4
3	76·9	97·4
4	90·8	—
5	104·8	—

the minimum was generally reached—the salivary index was 49% of normal with mucate and 53% of normal with sulphate of atropine. Two hours later, with sulphate it had returned to within normality (97%), but with mucate was still but 75% of normal, and in fact did not return to normal range for nearly two hours more. The equations tell us, in fact, that during the return to normal the salivary index increases on the average 14% of normal per hour with mucate and 22% of normal per hour with sulphate.

But for estimating the difference in time between returning to 60%, 70%, 80%, etc., of normality which occurred with the two drugs, the regression of x on y is a more useful instrument, thus:

Mucate : $x=0.06713y-2.15955$ ... C
Sulphate : $x=0.04351y-1.27754$ ... D

The number of hours after injection by which the salivary index had returned to 60, 70, and 80% of normal, as estimated from equations C and D, is shown in Table VII.

TABLE VII.—*Difference in Time of Returning to Specified Percentages of Normality with Mucate and Sulphate of Atropine*

Percentage of Normal	Hours after Injection		Difference (Hours)
	With Mucate	With Sulphate	
60	1·87	1·33	0·54
65	2·20	1·55	0·65
70	2·54	1·77	0·77
75	2·88	1·99	0·89
80	3·21	2·20	1·01
85	3·55	2·42	1·13
90	3·88	2·63	1·25
95	4·22	2·86	1·36
100	4·55	3·07	1·48

Thus, for example, if more than 25% depression of normality is regarded as essential for satisfactory drying of secretions before an anaesthetic, two hours represents the time latitude during which the anaesthetic should be administered with sulphate of atropine ; but with mucate an interval of almost three hours (2.88) may be permissible.

Conclusions

From the results it is clear that the peak of atropine effect, whatever the salt used, is reached about one hour after hypodermic injection. The effect then begins to wear off quickly, for the maximum action is not maintained more than half an hour beyond this. The intensity of the drying-up effect is somewhat greater in the case of the mucate, although even here only 54% depression of salivary activity occurs. It is clear, therefore, that 1/100 gr. (0.65 mg.) of either salt is in no way an excessive dose—the result being far from complete atropinization—let alone overdose. Since this dose is the one commonly employed throughout the world, it must be that the degree of partial atropinization produced is adequate in preventing excessive salivation during anaesthesia.

The results also explain the rarity of gross overdosage in infants to whom 1/200 gr. (0.32 mg.) atropine is commonly given. While 1/200 gr. probably produces an effect near complete atropinization, there are few accidents, because the adult dose of 1/100 gr. (0.65 mg.) is in reality on the small side.

In considering the duration of the atropine effect, the time taken for the subject to return to normal must be differentiated from the "clinical" or effective duration. In the former case the prolongation provided by mucate is of the order of two hours. However, the *clinical* duration is of more practical interest, and represents the duration of the anti-sialogogue action effective for the purpose of anaesthesia. The difficulty in assessing this, however, is in deciding what degree of depression of salivation would be effective. Suppose that a salivary depression less than 25% of normal is inadequate. The difference in duration of effect between the two drugs as shown in Table VII is nearly one hour. This coincides with our own clinical opinion, but is not in accord with the eight-hour effect described by Asquith and Thomas. They, however, used 1/75 gr. (0.87 mg.), and may have regarded higher levels of salivary activity as effective.

Clinical Implications

Saliva.—The clinical question which arises as a result of these experiments is whether atropine mucate offers any advantage over atropine sulphate in preparation for an anaesthetic. The answer depends on what is regarded as an effective level of salivary depression. This must vary with different anaesthetics, since they probably exert different stimulant effects on the salivary glands. In the case of nitrous oxide, for example, with which salivary stimulation is not great, 10% depression might be adequate. In this case the effective duration of mucate is 3.88 hours, compared with 2.63 hours with sulphate. In the case of trichlorethylene, where perhaps 25% depression might be adequate, the effective duration with mucate is now 2.88 hours, compared with 2 hours with sulphate. In the case of open ether, perhaps nothing less than 40% salivary depression might be effective. The difference in duration between the two salts is now only 30 minutes, since the mucate duration is 1.87 hours and the sulphate 1.33 hours. Whether these differences make the use of mucate worth while clearly depends on the opinion of the anaesthetist. It seems to us that the use of atropine mucate gives, in any case, rather more latitude in timing—a latitude depending probably on the anaesthetic to be used. The factor of difference in cost between the two salts seems to be very small, and can be discounted in hospital practice.

Pulse.—A brief bradycardia following an injection of atropine, before the pulse begins to rise, is well known clinically. Thus Shearer (1951), in a large series, found transient bradycardia fairly constantly, though with doses greater than 1/100 gr (0.65 mg.). That the occurrence of bradycardia is dependent on dose is also suggested by Waters (1938), who failed to observe this effect in three subjects after 1/100 gr. Some importance has been attached to the transient bradycardia of atropine. The drug is commonly administered to prevent the muscarinic effects of neostigmine when reversing the paralysis of curare-like drugs. Deaths have been reported in these circumstances when atropine and neostigmine have been given simultaneously, and have been attributed to the slowing effect of both drugs on the heart simultaneously. The intravenous administration seems to avoid the bradycardia (Hunter, 1953), but our own findings suggest that it is still a wise precaution to give the atropine at least 5 to 10 minutes before the neostigmine.

Summary

A method is described for measuring the amount of saliva secreted following a known stimulus. This has been used on volunteers to study the depression of salivary activity produced by atropine sulphate and atropine mucate (hyperduric atropine), and to determine the relative durations of action of these drugs. The results obtained are analysed and the clinical implications discussed. Observations made on the pulse rate during the experiments are also discussed in some detail.

We wish to thank Messrs. Allen and Hanburys for supplying the atropine used in the experiments.

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A.C.T.H. AND CORTISONE IN IDIOPATHIC THROMBOCYTOPENIC AND SCHÖNLEIN-HENOCH (ALLERGIC) PURPURA

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Several reports of the efficacy of A.C.T.H. and cortisone in idiopathic thrombocytopenic purpura and Schönlein–Henoch (allergic) purpura have been published. The results have been by no means consistent. The factors involved in their action have still to be clarified, and it is apparent that their precise status in the treatment of purpura has yet to be defined.

The following is a report of three cases of idiopathic thrombocytopenic purpura and a case of Schönlein–Henoch purpura treated with A.C.T.H. and/or cortisone. A brief review is included of reports so far available on the use of these hormones in haemorrhagic disorders.

Case 1

A girl aged 14 was admitted to Arbroath Infirmary on January 3, 1952, in an acute haemorrhagic state. Her periods had begun five months before admission, and during that time menstruation had been normal and regular. During the fortnight before admission there had been prolonged vaginal bleeding, epistaxis, and a tendency to bruise easily. There was no previous history of bleeding in the patient or her family, and no drugs had been taken recently. On admission she was severely exsanguinated, bleeding from nose, mouth, and vagina, and showing diffuse purpura and ecchymoses over her shins and feet. The spleen, which was not at first felt, later enlarged, and the tip became palpable a few days after admission. There was no lymphadenopathy. Blood examination on admission was as follows: Hb, 3.5 g.%; red cells, 1,980,000 per c.mm.; white cells, 9,900 per c.mm.; P.C.V., 15%; M.C.V., 76 μ^3; M.C.H.C., 35%; platelets, 70,000 per c.mm. A blood film showed a considerable number of polychromatophilic cells and a few normoblasts; a few myelocytes but no other primitive leucocytes were seen. Bleeding-time, 9 minutes; coagulation time (Lee and White), 9 minutes; Hess test, positive. Sternal puncture on January 4 showed a highly cellular reactive normoblastic marrow with numerous megakaryocytes. On these grounds a diagnosis of idiopathic thrombocytopenic purpura was made.

Despite transfusions of fresh blood—20 pints (11.4 litres) in 10 days—the haemorrhagic state continued, and on the fifth day after admission the bleeding-time had risen to 24 minutes. A.C.T.H., 25 mg. six-hourly, was begun on the seventh day, a total dosage of 375 mg. being given without clinical or haematological effect. On the eleventh day oral cortisone, 50 mg. twice daily, was started. A partial clinical response occurred, as shown by a lessening of blood loss, but the bleeding-time was still increased at 12–18 minutes and the platelet count remained low at 25,000–60,000. In view of this incomplete response, cortisone was stopped and splenectomy was carried out on the seventeenth day. This induced a satisfactory remission. Traces of bleeding from the nose or vagina occurred for a few weeks after operation and then ceased completely. Some fall in the bleeding-time was noted as early as the evening of operation, when a reading of 9 minutes was found. A week after splenectomy this had fallen to 4 minutes, and subsequently values between 2 and 3½ minutes were obtained. The platelets remained depressed for a week after splenectomy with counts ranging from 30,000 to 67,000 per c.mm. The count had risen to 210,000 per c.mm. two weeks after splenectomy and to 386,000 per c.mm. after three weeks. On her discharge from hospital on March 1 the blood showed: Hb, 9.8 g.%; red cells, 4,350,000 per c.mm.; white cells 5,500 per c.mm.; platelets, 500,000 per c.mm.; bleeding-time, 3 minutes; coagulation time, normal.

Comment.—In this patient A.C.T.H., 100 mg. daily, produced no effect. A partial remission, as evidenced by the reduced haemorrhage from the nose and vagina and the reduced rate of fall of haemoglobin, followed the administration of oral cortisone, 100 mg. daily. No change occurred in the bleeding-time or platelet count. Splenectomy induced a complete remission.

Case 2

A boy aged 5 was admitted to Arbroath Infirmary on January 16, 1952, with the history of continued bleeding from a tooth socket following extraction three weeks previously. During the same period there had been recurrent epistaxis. No previous abnormal bleeding had occurred in the patient or in the family, except in a female cousin who was said to be a "bleeder." No drugs had been taken before the onset of the illness. Physical examination showed a severe anaemia, with scattered petechiae and ecchymoses of the skin, and bleeding from a tooth socket and from the nose. The liver and spleen were not enlarged and there was no obvious lymphadenopathy. A blood examination resulted as follows: Hb, 5.5 g.%; red cells, 2,000,000 per c.mm.; white cells, 13,850 per c.mm. (neutrophils 53%, lymphocytes 35%, monocytes 5%, myelocytes 7%); platelets, 40,000 per c.mm.; nucleated red cells, 3 per 100 white cells; bleeding-time, 30 minutes; coagulation time (Lee and White), 4 minutes; Hess test, positive. An iliac marrow smear showed a highly cellular normoblastic marrow, while sections showed abundant megakaryocytes and promegakaryocytes and some increase in eosinophils. Leucopoeisis was slightly increased but normal. A diagnosis of idiopathic thrombocytopenic purpura was made.

Despite blood transfusions—6 pints (3.4 litres)—severe haemorrhage continued. Oral cortisone, 50–100 mg. daily, which was started on the sixth day after admission, produced no clinical improvement and no rise in the platelet count, which varied from 26,000 to 58,000 per c.mm.; the Hess test did, however, become negative and there was some fall in the bleeding-time. On the eleventh day the cortisone was stopped and splenectomy carried out. Following splenectomy there occurred a prompt and sudden fall in the bleeding-time, with cessation of all bleeding. Twenty-four hours after operation a transient but severe relapse occurred, with a recurrence of bleeding and a rise in bleeding-time. Thereafter progress was satisfactory, but the platelets did not begin to rise for three weeks, and normal figures were not reached until 28 days after splenectomy. On his discharge from hospital on February 28 the bleeding-time was 3 minutes and the Hb 11 g.%.

Comment.—In this patient oral cortisone, 50–100 mg. daily produced no improvement in the haemorrhagic state or in the platelet count. A slight fall in the bleeding-time coincided with the administration of cortisone, and the Hess test became negative.

Case 3

A woman aged 72 attended the blood clinic in Maryfield Hospital, Dundee, in April, 1952, with a complaint of a generalized petechial rash and scattered ecchymoses, beginning in January, 1952. Physical examination showed numerous petechiae and several ecchymoses, up to 2 in.

(5 cm.) in diameter and at all stages of resolution, on limbs and trunk, and one large mucous haemorrhage in the tongue, but was otherwise negative. Indeed, the patient was surprisingly fit and youthful in appearance. The spleen was not palpable. Investigation revealed all the haematological characters of idiopathic thrombocytopenic purpura, with a strikingly positive Hess test and no clot retraction in 24 hours. The initial platelet count was 30,000 per c.mm. and the bleeding-time over 35 minutes. At no stage was there significant anaemia, the initial Hb being 14 g.% and the red-cell count 4,500,000 per c.mm. The blood film was normal except for very scanty platelets, and the only marrow abnormality was a great excess of megakaryocytes, mostly immature, in the crusted fragments. Clotting-time and prothrombin concentration were normal. No drugs had been taken except ascorbic acid, administered without effect after the onset of symptoms, and there was nothing else of possible aetiological importance in the history. In spite of the patient's age, therefore, the diagnosis of idiopathic thrombocytopenic purpura was made.

After a control period of 14 days, during which symptoms and signs continued, treatment with A.C.T.H. was started; 40 mg. daily for three days followed by 80 mg. daily for seven days in divided six-hourly doses. By the fifth day of A.C.T.H., 80 mg. daily, the Hess test was negative, the bleeding-time had fallen to 8 minutes and the platelets numbered 45,000 per c.mm. On the seventh day bleeding-time was 15 minutes and platelets numbered 40,000. Treatment was then changed to oral cortisone, 25 mg. six-hourly, and within four days the response was complete, with a bleeding-time of 2 minutes and a platelet count of 250,000 per c.mm. Clot retraction became normal, and the marrow showed reduction in numbers of megakaryocytes. When the dose of cortisone was reduced, relapse of thrombocytopenia and bleeding-time occurred at once, and was well established within five days of stopping cortisone. On the ninth day without treatment the Hess test was also again positive. A second complete response took place on readministration of 100 mg. of oral cortisone daily, platelets reaching 370,000 per c.mm. in two days. The patient was discharged, being seen again two weeks after the second course of cortisone. Mild purpura had recurred, the bleeding-time was 17 minutes, and the platelets numbered 30,000 per c.mm.

Comment.—This patient showed partial response to A.C.T.H., 80 mg. daily, and reversal of all the features of the disease on two occasions with 100 mg. of oral cortisone daily.

Case 4

A girl aged 13 was admitted to the Royal Infirmary, Dundee, on March 20, 1952, with the complaint of a rash accompanied by abdominal pain, sickness, and loose offensive stools containing red blood during the previous week. Five weeks before this she had a sore inflamed throat, which was treated with penicillin. Following this she developed intermittent pain and swelling of the ankles and a rash confined mainly to the arms and legs. Her previous health had been good and there was no previous allergic history, either in the patient or in her family. She had undergone an operation for "obstruction of the intestine" when aged 5.

On examination she was listless, and complained of lower abdominal pain. A well-marked purpuric rash was present over the shoulders, arms, and legs, and only a few petechiae were seen on the chest, face, and limbs. Pustular lesions were present over both ankles and heels. The liver and spleen were not enlarged and there was no lymphadenopathy. The throat was red, but no exudate was present. The abdomen was tender in both iliac fossae, but no masses were felt. No abnormality was found in the heart or lungs. The stools contained red blood. Blood examination on admission gave the following results: Hb, 13.1 g.%; red cells, 4,700,000 per c.mm.; white cells, 9,200 per c.mm. (neutrophils 66%, lymphocytes 29%, monocytes 4%, eosinophils 1%); P.C.V., 37.5%; M.C.V., 89 μ^3; M.C.H.C., 35%; platelets, 520,000 per c.mm. A blood film showed no abnormality in the red or white cells except for an occasional "irritation" lymphocyte. E.S.R., 18 mm. (Wintrobe); bleeding-time, 3½ minutes; clotting-time, 5 minutes; Hess test, positive. Urine examination showed the presence of red blood cells, but no casts were seen. No intestinal pathogens were found on stool culture. *Staphylococcus pyogenes* and *Streptococcus viridans* were obtained from culture of a throat swab. The Widal reaction was negative.

A diagnosis of Schönlein–Henoch purpura was made and a small dose of A.C.T.H., 10 mg. twice daily, was started on March 26. A dramatic improvement occurred as early as 12 hours after treatment began; the abdominal pain and haemorrhage from the bowel stopped and the appetite returned. The intermittent pyrexia and tachycardia which had been present promptly disappeared with A.C.T.H. therapy and the purpura lessened, but the Hess test remained positive. After six days A.C.T.H. was stopped and a prompt relapse occurred, and there was again rapid improvement when the drug was restarted. The A.C.T.H. was replaced by oral cortisone, 12.5 mg. twice daily, on April 3 and no relapse occurred even when the cortisone was reduced to 12.5 mg. once daily. All drug treatment was stopped on April 9 and the patient was well when discharged from hospital on April 24. Since discharge her general condition has remained good, but small crops of petechiae have occurred and the Hess test has remained positive. There has been no recurrence of joint symptoms, abdominal pain, or intestinal haemorrhage.

Comment.—In this patient A.C.T.H., 10 mg. twice daily, produced a rapid improvement in the clinical condition with a disappearance of abdominal pain and intestinal haemorrhage and a lessening of the purpura. The Hess test remained positive. Oral cortisone, 12.5 mg. twice daily, maintained the improvement.

Discussion

During the last two years convincing evidence has accumulated that both A.C.T.H. and cortisone may increase capillary resistance, and also, according to the majority of reported studies, increase the platelet count and reduce the bleeding-time in idiopathic thrombocytopenia. In spite of this, reports of clinical trials of these hormones in purpuric syndromes have been by no means uniform, and neither the exact mode of action nor the type of case in which success may confidently be expected has yet been established. Robson and Duthie (1950) demonstrated an increase in capillary resistance in normal vessels after the application of various types of bodily stress. This increase is presumably mediated by adrenocortical stimulation as it follows the administration of A.C.T.H. They also reported response to short courses of A.C.T.H., including significant rises in platelets, in two patients with idiopathic thrombocytopenic purpura. Complete reversal of the haematological findings in this disease rapidly following the administration of A.C.T.H. or cortisone has been reported by Wintrobe (1950); by Bethell *et al.* (1951) in all seven patients treated; by Wightman (1951) in two cases; by Jacobson and Sohier (1952) in three cases; and by Evans and Liu (1951), who obtained two distinct responses in a severe case. On the other hand, Ragan (1951) found no change in the platelets in two patients who had relapsed after splenectomy with either cortisone or A.C.T.H., although the purpura was relieved; while of 10 patients treated in the M.R.C. investigation (1952) only five responded. Moreover, Spaet and Mednicoff (1951) quote unpublished negative results obtained by Dameshek and Stefanini in this disease.

The present report adds to the list one case (No. 3) which showed decrease of capillary fragility and purpura with A.C.T.H. without any effect, in the dosage used, on the thrombocytopenia; in another case (No. 2) oral cortisone had a slight similar effect, while in a third case no response occurred to A.C.T.H. and oral cortisone in doses of 100 mg. daily. One case (No. 3) responded completely to oral cortisone; there can be no doubt that remission was due to the hormone, as relapse rapidly followed its withdrawal, and

response to 100 mg. daily was again complete, with relapse following again on the second withdrawal.

The factors which determine success or failure with this treatment in thromboeytopenia are as yet far from clear. In some cases 100 mg. of A.C.T.H. daily has produced complete response. In other patients, such as Case 3 reported here and two cases described by Bethell *et al.*, A.C.T.H. produced improvement only in capillary resistance, while cortisone produced a complete response. A third group responded only symptomatically or not at all to both A.C.T.H. and cortisone. Dosage is probably important, as requirements may well vary widely from case to case. One case reported by Bethell *et al.* responded only when 300 mg. of cortisone was given daily, and the negative results in our Cases 1 and 2 may be due to inadequate dosage: the supply of cortisone was limited, however, and as these patients were seriously ill it was not advisable to delay splenectomy.

Bethell *et al.* suggest that patients failing to improve or relapsing after splenectomy, or those with megakaryocytic aplasia, will not respond to A.C.T.H. or cortisone (although the purpura may be improved symptomatically), and yet four cases are on record of response occurring in splenectomized patients who had relapsed (Bethell *et al.*, 1951; Evans and Liu, 1951; Jacobson and Sohier, 1952), so that presence or absence of the spleen can scarcely be a factor, unless the possibility of a hyperplastic spleniculus is admitted. Similarly, Wightman (1951) reported complete remission in one patient in whose marrow no megakaryocytes could be found. In general, however, successfully treated cases have shown megakaryocytic hyperplasia in the marrow.

So far there appears to be no report of successful use of these hormones in secondary or toxic thrombocytopenia, and Finch (1951) mentioned one failure in thrombocytopenia due to gold. However, two of the cases of allergic purpura described by Kugelmass (1951) had thrombocytopenia abolished by cortisone, and Evans and Liu ascribe the action of cortisone and A.C.T.H. in thrombocytopenia to the correction of an abnormal immunological response. In support of this explanation Evans and Liu cite evidence presented in the paper of Evans *et al.* (1951) for antithrombocyte activity in the serum in idiopathic thrombocytopenic purpura and for the aetiological relationship between this disease and acquired haemolytic anaemia. An actual thrombocytopenic factor, active in normal subjects, has been found by Harrington *et al.* (1951) in the serum of patients with thrombocytopenic purpura. Direct evidence for the effect of cortisone in relieving thrombocytopenic purpura artificially induced in rats by injection of antiplatelet serum was sought by Spaet and Mednicoff (1951), but with negative results. These authors favour the view that cortisone, when it acts in thrombocytopenia, does so by depressing antibody formation.

The duration of remissions in idiopathic thrombocytopenic purpura induced by cortisone and A.C.T.H. has in general been brief, but in some of the reported cases has lasted several months. The problem of maintenance dosage is discussed by Evans and Liu, who kept a patient "symptom-free" with 25 mg. of A.C.T.H. daily "in alternate weeks."

The Schönlein–Henoch syndrome is acknowledged to be an allergic disease, and our fourth patient was a girl of 13 who responded rapidly and completely to A.C.T.H. and cortisone. A feature of this case was the small dose of A.C.T.H. and cortisone (10–12.5 mg. daily) which prevented a relapse occurring. The weight of evidence at present supports the efficacy of A.C.T.H. and cortisone in this condition, and successes have been described by the following: Levinson *et al.* (1951) found a rapid response to 100 mg. of A.C.T.H. daily in a girl aged 15, but no effect on the renal manifestations; Morelli *et al.* (1951) described rapid improvement in a boy aged 8 with 30 mg. of A.C.T.H. daily, including improvement in the urinary findings; Portillo *et al.* (1951) described a dramatic response to 75 mg. daily in a girl aged 11 who was seriously ill after a control period in which all the symptoms had worsened; Kugelmass (1951) recorded four prompt responses in children aged 9–15 to cortisone, 200 mg. initially, followed by 100 mg. daily; and Stefanini *et al.* (1950), whose case showed a more delayed response (six days) with a dose of 15 mg. A.C.T.H. daily. On the other hand, Woolley (1952) found no response to 60 mg. of A.C.T.H. daily in a boy aged 3½, but his opinion that further use of the hormone in this condition is not justified would appear to be untenable in face of the evidence so far available.

Conclusions

There is experimental and clinical evidence that A.C.T.H. and cortisone can enhance capillary resistance and improve the symptom of purpura, both in the presence and in the absence of thrombocytopenia, and whether the latter, if present, is affected by the hormones or not.

A.C.T.H. and cortisone have been effective in reversing the haematological changes in idiopathic thrombocytopenic purpura in most reported studies, but the mode of action and the factors determining response are still obscure, and further studies are necessary. Cortisone has on the whole been more effective than A.C.T.H. in this condition. We concur with the view of Jacobson and Sohier (1952) that in idiopathic thrombocytopenic purpura the trial of A.C.T.H. or cortisone is of practical value under two conditions—as a preparation for splenectomy, and to tide a patient over a critical bleeding episode.

A.C.T.H. and cortisone have proved efficacious in the great majority of reported cases of Schönlein–Henoch purpura, and their use is justified, especially in severe cases, though once again more extensive observations are required.

In purpuric states, oral cortisone is probably preferable, as repeated injections may give rise to haematomata.

Summary

Three cases of idiopathic thrombocytopenic purpura treated with cortisone and A.C.T.H. are described. One showed partial response to A.C.T.H. and complete response to oral cortisone, 100 mg. daily. Another showed no response to A.C.T.H. and a doubtful response to oral cortisone in the same dosage. The other case showed no response to both A.C.T.H. and cortisone. These two latter cases responded to splenectomy.

One case is described of Schönlein–Henoch purpura which responded dramatically to small doses of A.C.T.H. and oral cortisone.

The literature relating to the use of A.C.T.H. and cortisone in these conditions is briefly reviewed.

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POLYARTERITIS NODOSA TREATED WITH A.C.T.H.

REPORT OF A CASE, WITH RECOVERY

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For some years it has been suspected that polyarteritis nodosa is by no means uncommon. The disease manifests itself in many forms, and an excellent review of the clinical features is provided by Miller and Daley (1946). As these authors infer, in many cases the condition presents in a manner extremely difficult of diagnosis, and, though suspected, it most frequently remains unproved. They estimate the mortality rate to be well below 50%, but, even so, it must still be accounted a formidable disease. Probably the majority of cases recover spontaneously, and this factor renders hazardous the assessment of any particular form of treatment, particularly as reference to a substantial series of cases is difficult to find. Lovshin and Kernohan (1949) collected only 29 cases in a search through the records of ten consecutive years at the Mayo Clinic.

A.C.T.H. and cortisone have been used in treatment by a number of workers. Mundy *et al.* (1951) give a full account of one case, complicated by asthma, treated at first with a series of short courses of A.C.T.H.; each course lasted a week and was succeeded by improvement which was in part subjective (for example, relief of asthma), but in part objective (for example, recovery of muscle power and subsidence of E.S.R.). Treatment suppressed rather than eradicated the disease, and the patient was subsequently kept on maintenance treatment with intramuscular and oral cortisone. Drury *et al.* (1951) published a single case treated with cortisone. Although their patient was desperately ill, and died six days after treatment was started, there was suggestive histological evidence of retrogression of some of the arterial lesions. This was observed also by Shick *et al.* (1951), who treated 13 cases with A.C.T.H. and cortisone. The dosage of A.C.T.H. was inconstant owing to a temporary shortage. Clinical improvement was marked by early subsidence of fever and more gradual decrease of E.S.R. Two patients died, and in most there was evidence of residual vascular damage. These authors claim no more than remission of the disease process from use of A.C.T.H. and cortisone. They advise early, intensive, and prolonged treatment.

Case History

A 15-year-old schoolboy was admitted to hospital on April 10, 1951. In the previous January he developed a fever accompanied by a purpuric eruption of the legs. The fever subsided, but there followed recurrent crops of purpura on the limbs which lasted a few days and left a brown staining of the skin. Occasional attacks of vomiting with generalized colicky abdominal pain were noted, and on one occasion a haematemesis followed by melaena was observed. In February there was a short-lived bout of frank haematuria, which was not repeated. Admission was requested on account of recurrent purpura, three weeks' persistent fever, and pain in the muscles of the upper arms, thighs, and calves. His illness had been marked by loss of over one stone (6.35 kg.) in weight.

Examination showed an intelligent, co-operative lad who had evidently lost flesh recently; temperature 100° F. (37.8° C.). There was a purpuric eruption on the thighs and genitalia, and post-purpuric staining of both arms, especially the elbows; no significant adenopathy; no nodules. Pulse, 120 a minute; sinus rhythm; heart sounds normal; B.P. (resting), 160/90; electrocardiogram normal. The abdomen showed no clinical abnormality; liver and spleen were not felt. The C.N.S. was normal, as were the optic fundi. There was no evidence of peripheral neuritis, and the chest was clear.

Investigations.—Haemoglobin, 66%; red blood cells, 4,260,000 per c.mm.; leucocytes, 9,800 per c.mm. (neutrophil polymorphs 78%, lymphocytes 19%, monocytes 3%); stained films showed no abnormal cells; platelets were plentiful; clotting-time, 3 minutes 25 seconds; bleeding-time 5 minutes 45 seconds; blood culture, sterile in three separate specimens; E.S.R. (Westergren), 75 mm. in one hour. The plasma proteins totalled 8.75 g. per 100 ml. (albumin 4.6 g., globulin 3.55 g., fibrinogen 0.6 g.), and serum agglutinations were negative in the enteric group and *Brucella abortus*.

The urine contained a large amount of albumin, and a centrifuged deposit showed 5 leucocytes and 10 red blood cells per high-power field; culture was sterile. Radiographically the lungs were clear. The capillary resistance test was negative.

Treatment.—Within a week of admission a crop of subcutaneous nodules appeared, some of which were tender. Excision of one of these resulted in arterial spurting. The pathological report (Dr. Morgan Hall) was: "Section of the biopsy specimen shows a small artery in which there is hyaline necrosis of the subendothelial tissue and of the inner media and irregular necrosis of the outer media. The lumen is filled with thrombus. There is dense inflammatory infiltration, mostly acute, in the adventitia and perivascular tissue. The histological picture is characteristic of the acute arteritis and periarteritis of polyarteritis nodosa." During this week there were recurrent attacks of abdominal colic, with no localizing signs, and vomiting. The vomitus contained small quantities of blood. There was, in addition, diarrhoea with streaks of bright-red blood. Fever persisted, there was marked generalized muscular tenderness, and the patient was accounted gravely ill. For these reasons treatment was started with A.C.T.H., 15 mg. six-hourly for three weeks, the dose then being reduced to 15 mg. twelve-hourly. This was continued for a further three months, when it was reduced to 15 mg. daily, after one week of which all treatment was stopped. The dosage of A.C.T.H. was regulated on the basis of his response to treatment as judged by the following criteria: (1) subjective improvement; (2) subsidence of fever; (3) disappearance of subcutaneous nodules and purpuric spots; (4) disappearance of blood from urine; (5) gain in weight; (6) lowering of blood pressure and pulse rate to normal; and (7) decrease of E.S.R. to normal.

Progress.—His response, as judged by factors (1), (3), and (5) above, was immediate. Fever subsided within three weeks and the quantity of blood in the urine steadily diminished. The E.S.R. decreased very slowly, but by August 21 it was 14 mm. in one hour. The blood pressure also dropped only slowly, but on July 26 it was 130/90, and thenceforward remained at a normal level. On August 25, the 140th day in hospital, he was transferred to a convalescent home. He had gained 25 lb. (11.34 kg.) in weight while in hospital. There were no untoward effects of treatment, no fluid retention, and no psychic disturbance. He did, however, develop a mild degree of "moon-face."

This boy has been seen and examined at regular intervals as an out-patient. He has had no symptoms since discharge,

and sixteen months have now elapsed from that date. In that time he has gained over 26 lb. (11.8 kg.) in weight. There remains only faint staining of the skin over his elbows and a minute trace of albumin in the urine, the centrifuged deposit containing no abnormality. His blood pressure and E.S.R. are normal. He has completed his schooling, and is an apprentice in a sheet-metal factory.

Discussion

Although the history and clinical findings were characteristic of polyarteritis nodosa, we were fortunate in obtaining early histological proof of the diagnosis. The absence of polymorphonuclear leucocytosis and eosinophilia does not confound the diagnosis, for Miller and Daley (1946) state that the former finding occurs in 70% of cases, whilst eosinophilia is relatively unusual, being found in approximately 20%. Our patient gave no antecedent history of a specific infection or of upper respiratory tract infection, and he had taken no drugs before his illness.

It cannot be stated categorically that he would not have recovered spontaneously, though the clinical course certainly suggested otherwise. There is no doubt that improvement dated from the beginning of treatment with A.C.T.H. and, furthermore, that from that time a prolonged remission was established. The plan of treatment differed from that set out by Mundy *et al.* (1951) in that a prolonged consecutive course of A.C.T.H. was given, and was continued until all clinical and laboratory signs of activity had subsided. Whether the patient can be regarded as cured can be determined only by prolonged surveillance.

Summary

A case of polyarteritis nodosa in an acute phase is presented, with clinical and pathological findings. Treatment was provided with intramuscular A.C.T.H., which was continued until no clinical or laboratory evidence of activity was forthcoming.

Complete remission of the disease process for over one year to date has been achieved.

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Rabies is still an acute problem in many parts of the world where dogs are often in contact with wild animals. The World Health Organization's Expert Committee on Rabies has been meeting in Rome this week to examine new developments resulting from large-scale experiments in rabies control sponsored by W.H.O. in Spain, Greece, Yugoslavia, Mexico, and other countries. In this second session in three years the Committee has discussed various improvements in types of vaccines for human and veterinary use. The success of canine vaccination in many countries, including the United States, has been reviewed, and the Committee has received reports on systematic treatment with hyperimmune serum in Iran among people bitten by rabid wolves, and on the local treatment of wounds in laboratory animals in Spain. Another task of the Committee was the final approval of the text of the W.H.O. *Manual of Laboratory Techniques in Rabies*, which is designed to standardize laboratory procedures and facilitate comparison of international experiments. Training courses and meetings are organized by W.H.O. to spread information on new and effective techniques of rabies control throughout the many countries which, unlike England, Switzerland, and the Scandinavian countries, have been unable to achieve complete control of the disease.

COMPOSITION OF ARTICULAR CARTILAGE IN OSTEOARTHRITIS

CHANGES IN COLLAGEN/CHONDROITIN-SULPHATE RATIO

BY

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The bluish-white hyaline cartilage of healthy articular surfaces is a smooth, glistening, and resilient tissue, and it is here that the earliest morphological changes characterizing osteoarthritis or degenerative joint disease appear. Opaqueness and yellow discoloration accompanied by progressive loss of elasticity are evidence of senescent change preceding the appearance in the surface layer of small blisters, grooves, and pits. Later, as larger circumscribed erosions approach the underlying bone, the articular surface assumes a velvety appearance and spongy texture resulting from loss of intercellular substance and exposure of collagen fibres. Histologically, the affected cartilage is cleft along its fibrillary planes, and, since the superficial fibres are tangentially arranged, the earliest lesion is horizontal flaking of the surface cartilage. Ultimately, as extension along the path of radially disposed collagen bundles occurs, splitting and the concomitant loss of tissue result in exposure of subchondral bone. Fibrillation, as this process is known, is the hall-mark of osteoarthritis.

These changes occur first and foremost in weight-bearing joints. In the knee, fibrillation of articular cartilage occurs principally in those areas in which weight-bearing is concentrated, and which are most subjected to shearing stress (patella, exposed portions of the tibial condyles, patellar surface of the femur, and the anterior and middle thirds of the medial femoral condyle) (Bennett *et al.*, 1942).

Little work has been devoted to chemical aspects of fibrillation. Preliminary data (Matthews, 1952), dealing with the proportions of the two main organic components of healthy articular cartilage, indicated the importance of mechanical function in determining the ratio of collagen to chrondroitin sulphate. Using similar chemical methods, we have investigated this ratio in fibrillar articular cartilage compared with that of healthy cartilage within the same joint.

Materials and Methods

The material was taken at necropsy. A knee-joint was opened, and, after flexing the joint fully, the articular surface of the lower end of the femur was inspected for fibrillar lesions. Knee-joints showing frank degenerative change more than fibrillation were not used, since they yielded insufficient material for analysis.

The areas selected for this investigation, therefore, were moderately advanced circumscribed lesions, about 2–3 cm. in diameter, showing fibrillation with loss of superficial cartilage, and affecting the medial condyle and the patellar surface of the femur, or the medial condyle alone. The whole of the fibrillar material constituting the lesion was excised with a sharp scalpel, care being taken to exclude the healthy adjacent and underlying articular cartilage. For control material, a piece of healthy cartilage of similar area and thickness was pared from a corresponding site on the

lateral femoral condyle. When fibrillar cartilage was taken from the patellar surface of the femur, healthy cartilage was also removed from an adjacent area. Cartilage from the weight-bearing areas of the medial and lateral condyles and from the patellar surface of the femur of healthy adult knee-joints without fibrillation served as a further control. Cartilage samples obtained in this way were finely divided with a scalpel, dehydrated in several changes of acetone, and finally dried over concentrated sulphuric acid *in vacuo* to constant weight. Determinations of collagen and chondroitin sulphate on aliquots were carried out as previously described (Matthews, 1952).

Results

The accompanying table gives results obtained from seven knee-joints showing twelve comparisons between fibrillar and healthy cartilage. Five joints showed lesions of both medial condyle and patellar surface, while in two the medial

Collagen and Chondroitin Sulphate Content of Fibrillar and Healthy Articular Cartilage in the Knee (% of Dry Weight)

Case	Age	Hydroxyproline as Collagen	Hexosamine as Chondroitin Sulphate	Collagen/Chondroitin-sulphate Ratio	Mean of Ratios	Hydroxyproline as Collagen	Hexosamine as Chondroitin Sulphate	Collagen/Chondroitin-sulphate Ratio	Mean of Ratios
		Fibrillar Cartilage: Weight-bearing Surface of Medial Femoral Condyle				Healthy Cartilage: Weight-bearing Surface of Lateral Femoral Condyle			
1	42	53·3	13·2	4·0		45·0	21·6	2·1	
2	49	62·3	14·8	4·2		52·5	20·8	2·5	
3	64	56·3	20·0	2·8	3·67	50·3	26·0	1·9	2·09
4	68	51·8	20·0	2·6	s.d.	45·0	23·2	1·9	s.d.
5	68	62·3	10·4	6·0	1·18	54·0	22·0	2·5	0·33
6	78	52·5	16·8	3·1		45·8	21·6	2·1	
7	81	47·3	15·6	3·0		44·3	27·6	1·6	
5 control cases without fibrillation aged 45–75		Weight-bearing surface: medial femoral condyle			1·94 s.d. 0·09	Weight-bearing surface: lateral femoral condyle			2·10 s.d. 0·07
		Fibrillar Cartilage: Patellar Surface of Femur				Adjacent Healthy Cartilage: Patellar Surface of Femur			
1	42	60·0	15·7	3·8		48·0	20·4	2·4	
3	64	57·8	18·4	3·1	5·16	54·8	22·0	2·5	2·34
4	68	50·3	8·4	6·0	s.d.	53·4	21·5	2·5	s.d.
5	68	60·8	9·2	6·6	2·54	53·2	23·0	2·3	0·20
6	78	60·8	9·6	6·3		50·2	25·0	2·0	
5 control cases without fibrillation aged 45–75		Patellar surface of femur			2·12 s.d. 0·07				

condyle only was affected. Additional results obtained from five control subjects whose ages ranged from 45 to 75 years, and in whom there was no evidence of fibrillation within the knee, are included.

It is evident that in fibrillar lesions of articular cartilage in the knee the collagen/chondroitin-sulphate ratio is greater than in healthy cartilage from the same joint; the ratios obtained for the latter agree well with those found for comparable sites in healthy joints.

The water content of the samples analysed was not determined. This value was readily obtained for smooth, healthy articular cartilage; but in fibrillar material, where a variable amount of extraneous water is held in the interstices, the true state of hydration is difficult to determine.

Discussion

The present-day morphological concept of fibrillation gains support from chemical analysis: the increased collagen/chondroitin-sulphate ratios found (as compared with healthy cartilage) reflect chemically the different rates of loss of these substances in cartilage undergoing fibrillation. As continued loss of cartilage tissue occurs, the more durable collagen fibres, though architecturally deranged, are lost at a slower rate than matrix substance. Although to the naked eye the areas of fibrillar cartilage analysed were of approximately similar severity, the ratios showed marked variation. Histological evidence of variation in the degree of fibrillation could not be obtained because the entire material removed was needed for analysis. It is conceivable, however, that, as the fibrillation process evolves, the extent to which inter-collagenous matrix is lost is variable from lesion to lesion.

Fibrillar lesions of cartilage are an expression of injury (Collins, 1949). Though it cannot be stated that fibrillation is initiated by mechanical factors alone, it is clear that once a breach has occurred in a smooth articular surface they then become potent pathogenic stimuli. The results reported therefore throw no light on the earliest chemical changes which must occur in articular cartilage before even incipient evidence of fibrillation appears.

While the nature of this early change remains unknown, it is reasonable to suggest that it primarily involves chondroitin sulphate. Thus Benninghoff (1925a, 1925b) concluded from histological studies that depletion of matrix (containing chondroitin sulphate) renders the superficial cartilage and its bared fibrils vulnerable to pressure, permitting the development of both circumscribed defects and generalized flattening. In normal cartilage Hirsch (1944) has emphasized the importance of chondroitin sulphate in maintaining elasticity; and Matthews (1952) has shown that in normal weight-bearing or mechanically stressed cartilage the proportion of chondroitin sulphate is increased. Conversely, in patellar articular cartilage undergoing fibrillation, loss of resilience is accompanied by a diminution in mucopolysaccharide content (Hirsch, 1944). Once initiated, the evolution of fibrillation is the result of a vicious circle in which loss of chondroitin sulphate leads to decreased resilience, which in turn facilitates the mechanical perpetuation of the process.

I wish to thank Dr. E. G. L. Bywaters, who suggested this work, and Dr. L. E. Glynn and Dr. R. Consden for their help and guidance.

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Medical Memoranda

Diabetic Coma Associated with Lipaemia and Complicated by Uraemia

Although many cases of lipaemia associated with diabetic coma have been reported, the following case is of interest because of the marked degree of lipaemia attained, with the manifestation of lipaemia retinitis, and also because of the unusual feature of temporary kidney dysfunction.

Case Report

A married woman aged 22 was admitted to hospital on August 9, 1951, deeply unconscious, with a history that, since an apparently normal pregnancy ten months previously, she had been complaining of weakness, and for the past three weeks of loss of weight and polyuria. She had been unconscious for about ten hours before admission.

On examination the patient could not be roused by painful stimuli. Her temperature was subnormal. A pustular rash was present over the extensor surfaces of the knees and elbows, consisting of raised yellowish white nodules, 2 to 3 mm. in diameter, with an erythematous periphery. Her blood pressure was 70/50. The pulse was 102 regular, and of fair volume. The pupils were small and reacted equally to light; corneal reflexes were absent. All tendon reflexes were absent. The extremities were flaccid. Fundi: the disks were normal; all vessels presented a waxy-white

appearance with the vessel walls clearly defined. No abnormalities were found in the respiratory system or gastro-intestinal tract.

Investigations.—Haemoglobin, 61%; W.B.C., 26,000 (5,200 monocytes). Urine contained albumin, and the sediment showed scanty granular casts. Benedict's test, orange. Rothera's test strongly positive. Blood sugar, 600 mg. per 100 ml.; blood urea, 50 mg. per 100 ml. In view of the appearance of the fundi, which were strongly suggestive of lipaemic retinitis, the following investigations were carried out: serum free cholesterol, 220 mg. per 100 ml.; serum ester cholesterol, 710 mg. per 100 ml.; serum total lipoids, 7.84%. The blood serum was of a whitish, opalescent, milky appearance, and became solidified as it cooled to room temperature. Lumbar puncture: despite the fact that the cerebrospinal fluid was cytologically and biochemically normal, apart from an elevated sugar fraction, it also presented an opalescent slightly "milky" appearance.

An intravenous drip of normal saline was started, and intravenous insulin given, 1,600 units during the first five hours, after which she became conscious of her surroundings and was able to answer simple questions, though she remained very drowsy, with marked hyperventilation. Her blood sugar was 480 mg. per 100 ml. The next day there was no material change in the level of consciousness, and hyperventilation was still in evidence. An electrocardiogram showed pronounced inversion of the T waves in leads I and CR_4, which, together with her continuing hypotension, was regarded as indicative of hypopotassaemia. Potassium was given by mouth and her general condition greatly improved, though the serum potassium twenty-four hours later was still only 15.7 mg. per 100 ml. By this time her E.C.G. tracings were normal and her blood pressure had risen to 110/80. Great disparity was observed between the blood and urinary sugar levels. Although her blood sugar was at times almost 600 mg. per 100 ml. there was never more than 1% sugar detectable in the urine, and quite often the urine proved to be sugar-free. Further, her output of urine was very small, and her blood urea steadily rose to a maximum of 180 mg. per 100 ml. nine days after admission, with gradual deterioration in her general condition.

Treatment was continued, her daily requirements of insulin, given with reference to frequent blood-sugar estimations, remaining very high. Her blood-urea level persisted unchanged for the next 10 days, after which it slowly declined to normal, accompanied by an increase in urinary output, the disappearance of the hyperlipaemia, a return of the renal sugar threshold to normal, and much improvement in her general condition. Her ultimate requirements of insulin proved to be 30 units a day. On discharge, after nine weeks in hospital, her blood urea was 35 mg. per 100 ml. and serum total cholesterol 213 mg. per 100 ml.

When seen six months after discharge her condition remained satisfactory.

We would like to thank the Department of Pathology, Dudley, Stourbridge, and District Group, for the investigations made on this patient.

S. Z. KALINOWSKI, M.D.
J. MILES WALKER, M.B., Ch.B.

Torsion of the Gall-bladder

Torsion of the gall-bladder seems to be rare enough to warrant the recording of a further case. Only about 80 cases have so far been reported in the literature since Wendel's original description in 1898, and most of these were in foreign countries. Rendle Short and Paul (1934) found only 50 cases, to which they added three. Krabbel (1920) and Kettner (1930) reported a correct pre-operative diagnosis in each of their two cases, but in spite of the striking clinical picture others do not seem to have emulated their example. A prerequisite of the condition is an unusual anatomy of the gall-bladder, surrounded on all sides by peritoneum and hanging free in the peritoneal cavity by a mesentery attached to the anterior border of the liver. Caldwell (1950) makes arteriosclerosis a possible additional predisposing factor in that the cystic artery may become tortuous and encourage rotation of the organ.

The twist is either clockwise or anti-clockwise. It has been suggested that, if the former, peristalsis of the colon may be responsible; if the latter, then peristalsis of the stomach may initiate the rotation. The age incidence is from 11 to 84 years, but most of those suffering torsion have been between 60 and 80. The clinical picture is very striking, and the case recorded followed the usual pattern except that no mass was felt.

CASE REPORT

A married woman aged 65 was admitted at 9.30 p.m. on September 5, 1951, with severe colicky abdominal pain. She had been well until 8 p.m., two days previously, when she complained of the sudden onset of right-sided abdominal pain, and vomited. The pain was felt in the R.I.F., and there had been colicky exacerbations of intensity. From the onset of the pain until admission she vomited four times. Since the pain had started there had been constipation and anorexia. She complained of right shoulder pain, for one hour only, prior to admission. There was no urinary upset.

Her temperature was normal and pulse rate 82. Examination of the abdomen revealed extreme tenderness from the region of McBurney's point upwards towards the right hypochondrium. The patient would scarcely allow the abdomen to be touched, but there was no rigidity. No mass was felt. Rectal examination revealed nothing abnormal. A diagnosis of acute appendicitis was made, and the abdomen was first opened by a gridiron incision not long after admission. There were many adhesions in the region of the appendix, but that organ showed no signs of recent inflammation. Appendicectomy was performed. In the upper angle of the wound a globular cystic swelling was palpated, and when a retractor was put into position this swelling was found to be black and running upwards as far as could be felt or seen. Gangrene of the gall-bladder was assumed and the abdomen was closed in the R.I.F. and reopened by a right Kocher's subcostal incision. A gangrenous gall-bladder was confirmed, and the cause was found to be torsion at its neck by one and a half turns in an anti-clockwise direction. The twist was reduced and an easy cholecystectomy performed. The organ was found to have its wall grossly thickened by oedema and contained an almost black fluid. A drainage tube was passed down to the ligated cystic duct and the abdomen closed.

The patient made an uninterrupted recovery, and was discharged on the twelfth post-operative day.

Pathological Report.—"Specimen of gall-bladder received with black oedematous walls measuring 4½ by 2 by 1½ in. (11.4 by 5 by 3.8 cm.). The wall was soft and spongy, and was ¼ in. (6 mm.) thick. The gall-bladder showed no evidence of previous inflammation, though a few small gritty pigment stones were present. Sections were taken of the neck of the gall-bladder, together with the cystic artery, and another of the artery itself just distal to the site of ligation. The histology showed complete infarction of the gall-bladder and the artery showed no atheroma."

I discussed this case with Mr. S. Chambers, then senior surgeon to the hospital, and he told me that he had seen two such cases in his 30 years as surgeon at the hospital. The last one occurred eight months previously.

I have since heard from Mr. Raymond Purvis that in July, 1946, he operated on a woman aged 84 whose torsion came on while she was sitting quietly in a chair.

I wish to record my thanks to Mr. R. Purvis, surgeon to the Royal South Hants Hospital, for permission to publish this case, admitted to one of his beds in the hospital.

E. W. O. SKINNER, F.R.C.S.Ed.
Lieutenant-Colonel, R.A.M.C.

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Reviews

THE E.M.S.

Medical History of the Second World War. Volume II: Emergency Medical Services. Edited by Lieutenant-Colonel C. L. Dunn, C.I.E., I.M.S.(ret.). (Pp. 492; illustrated. £2 10s.) London: H.M. Stationery Office. 1953.

The main value of Volume II, like that of the equally instructive and interesting Volume I,* is that it places on record some of the achievements and the mistakes of the Emergency Medical Services in the second world war. Careful study of these two volumes could obviate the need to learn afresh important lessons from the beginning in any future emergency.

One is tempted to suggest beginning at p. 195; the 300 subsequent pages are about the air-raids on industrial centres, including London, and they bring to life the true nature of civil defence. They are therefore particularly instructive for those readers who must now study such problems without previous personal experience of civil defence in action. They show how the E.M.S. organization functioned under heavy attack and in slack periods: examples are given of every field of E.M.S. activity and are amplified by the recorded impressions of many who played their part in those difficult days. Some of the personal contributions reach a high standard of descriptive writing. Thus, the report by the medical officer of health of the Borough of Bromley (pp. 265–271) shows vividly the vital part played in civil defence by the local sanitary authorities. Indeed, one of the thoughts which recurs repeatedly on reading this volume is that, important though the hospital casualty services are, they are only a part—and perhaps the easier part—of civil defence. This leads to the question whether the tripartite National Health Service, with its divorce of hospital from health authority service, is not a potential source of weakness for future civil defence organization. Professor de Wesselow, group officer for Sector 8, whose headquarters were based in the Surrey County Council Hall, Kingston, says (p. 248) that he considered the liaison between hospital service and civil defence services was not fully effective in the inner zone, though in the outer zone it was excellent largely because his headquarters were in the same building as Group 9 Civil Defence Headquarters. Such comments draw attention to the paramount importance of efficient liaison between hospitals and the other parts of the civil defence organization.

The same lesson runs through the first 191 pages, which depict the pattern of the E.M.S. in Scotland and Northern Ireland. It is interesting to see how Scottish and Ulster E.M.S. experience in essential matters—despite certain differences in composition and administration—paralleled that of England and Wales. The medical history of the Emergency Medical Services of the second world war shows clearly how in all four countries the E.M.S. paved the way to much of the National Health Service, especially in connexion with the following: development of rehabilitation and of blood transfusion services; expansion of hospital service by new construction; distribution of specialist staff among peripheral hospitals; and, above all, the welding of a heterogeneous collection of independent hospitals into one organization in which they still preserved a reasonable degree of individuality.

To the medical reader a main reflection, on laying down this fascinating history of the E.M.S., is that for both peace and war the present National Health Service hospital organization gives a hospital service much more adequate in itself than that of 1938. But great care must be taken to continue and strengthen that liaison between hospitals and local authorities which formed such a valuable part of the civil defence services in the second world war.

W. G. PATTERSON.

*Reviewed in a leading article in the *Journal* of November 1, 1952 (p. 984).

TREATISE ON PATHOLOGY

Reaction to Injury: Pathology for Students of Disease. By Professor Wiley D. Forbus, M.D. Volume 2: Reactions of Submission and Adaptation and the Disease Entities Arising out of their Elaboration. (Pp. 1,110; 83 illustrations, 54 of which are in colour. £7 10s.) London: Baillière, Tindall and Cox. 1952.

The first volume of this book, written by the professor of pathology of the Duke University, North Carolina, has already been reviewed in these columns (*Journal*, December 16, 1944, p. 792). The two volumes together constitute a comprehensive and weighty treatise on general pathology which has "cost the author a substantial part of 20 of the most active years of his life." He was inspired to write it by W. G. MacCallum, under whose guidance he became interested in pathology. It is constructed in the belief that the essential element in disease is the reaction of the individual to his environment, and that he is "capable of reacting in only three essential ways, (1) by resisting, (2) by submitting, and (3) by effecting an adaptation." These three reactions are taken to be the basis of disease. On this bold generalization, the first volume described "reactive reactions," and the author discussed exhaustively acute and chronic infections. The present volume is concerned with "submissive and adaptive reactions." The first part covers the changes usually described as retrogressive and produced by poisons and vitamin deficiencies. Then follow long sections on disorders of the erythron, diseases of the endocrine organs, the pathology of growth, and development of neoplastic diseases. The last part of the book, on adaptation to injury, is concerned with diseases of the circulatory and respiratory systems and the effects of obstruction in hollow viscera.

These two heavy volumes cost £10 18s. 6d. The weight and cost are largely due to the exhaustive, almost encyclopaedic, treatment of the subject, but in both volumes, more especially in the second, a considerable amount of space is taken up by a highly commendable and successful attempt to correlate morbid anatomy and histology with clinical signs and symptoms. No time, trouble, or expense has been spared in the preparation of the illustrations, which are plentiful, most of them being exceptionally good and some superb. The paper is of fine quality. In defending the high price of the book, the author points out in his preface, addressed in this regard to his American readers, and based on the cost of joyful living in their country, that the book "costs the student the price of three steak dinners, the price of enough gasoline to run his automobile three weeks," or "the price of a theater and dinner date with his best girl."

All books of this size suffer from a defect for which the author cannot be blamed: they cannot include important discoveries made during the long period of final preparation for publication. The book will certainly appeal to serious students of pathology. It is easy to read, and the style is simple and direct. It is not likely to be popular with undergraduates in Britain, because of its size and price and the wealth of detail it contains, especially when this is viewed against the background of our overweighted undergraduate curriculum.

GEOFFREY HADFIELD.

BEGINNING SURGERY

An Approach to Clinical Surgery. By Professor G. H. C. Ovens, O.B.E., M.B., B.S.(Lond.), F.R.C.S. (Pp. 309; 118 illustrations. £1 2s. 6d.) London: J. and A. Churchill. 1953.

In France the medical student does clinical work throughout the whole of his course of study, but this method, though it has some advantages, is not accepted in Great Britain. It follows that, after spending two or more years in the dissecting-room and laboratory, the student is suddenly brought face to face with patients who are ill and need sympathy and help rather than to be examined by a raw novice of the medical craft. At most medical schools it

is customary to give a short preparatory course for the student before he enters the wards, and there are some books which give written instructions on the same lines, though they are often too advanced for the beginner. This book by Professor Ovens gives exactly what is required by the student who is beginning his clinical surgery, and is obviously the result of many years of practical teaching. It has 10 pages of general introduction, 90 pages on general principles, and 200 pages on how to take notes and how to examine patients.

The introductory ten pages are packed with excellent and wise advice which should be read and re-read by every student.—"You are dealing with a particular patient, not with a case or specimen." "Do not try to read too much at this stage of your career." "Beware of being carried away by the new, the spectacular, and the unusual." "The first patients you deal with yourself, those who come under your care during your first clinical appointment, will make far more impression on you than most of the many thousands you will see later on."—These are pieces of advice which cannot be repeated too often to the beginner. The 90 pages on general principles—inflammation, wounds, haemorrhage, shock, etc.—give the simplest yet clearest account that we have ever seen. The last part of the book describes how a history should be taken and how to make a general and local examination of the patient; it should prove an invaluable guide to the student.

The book is written in a simple and attractive style. Every sentence has its definite message and there are no wasted words. We would like every medical student and every nurse to read it. They could not fail to profit by so doing.

ZACHARY COPE.

EPIDEMIOLOGY OF HEALTH

The Epidemiology of Health: A New York Academy of Medicine Book. Iago Galdston, M.D., editor. (Pp. 197. $4.) Published by Health Education Council, New York and Minneapolis. 1953.

This is an important book. It is based on the papers read at the eleventh Annual Eastern States Conference, has the distinction of being issued by the New York Academy of Medicine, and contains contributions from leading experts in epidemiology in the United States. We are so apt to associate epidemiology with the comprehensive investigation of epidemic diseases that the title at first sight seems a contradiction in terms. The Greek derivation of epidemiology, "a discourse upon crowds or people in the mass," shows the correctness of the word in its present connexion.

The authors are careful to explain that health is much more than the absence of disease. As the editor remarks:

> "The epidemiology of disease rests upon pathology and its associated sciences of bacteriology and toxicology, while the epidemiology of health rests upon normal physiology and its associated sciences of growth, development, and performance."

Proceeding from this premise, the authors in attempting to define health unexpectedly find themselves aground on the shoals of disease. Dr. Alton S. Pope's chapter on "Tuberculosis as a Study in the Epidemiology of Health" is really an excellent account of the epidemiology of tuberculosis, although it is perfectly true that the incidence and mortality of tuberculosis are an index of a community's health.

Special attention should be given to Professor John E. Gordon's three chapters on the "Evolution of an Epidemiology of Health." His historical review, like that of Professor O. Temkin in Chapter 2, is most interesting. But here again much of his attention is perforce devoted to the study of disease in the mass, the holistic point of view with mass disease interpreted on the basis of all factors involved—those of the host, the agent of disease, and the environment. Professor Gordon cautiously leads us on to consider health and disease as complementary functions that add up to a total situation, and even rejoices the statisticians with a mathematical formula of health. But, along with his colleagues in this book, he admits that we are only now beginning to study the epidemiology of health, although he adds: "The essential knowledge may well be forthcoming in the many studies of whole populations now so much a feature of epidemiologic practice."

In other chapters, Major-General G. E. Armstrong tells us how the United States Army practises the epidemiology of health; Dr. Leo Price describes the epidemiology of health in industry, which America has done so much to foster; Dr. E. Lindemann treats of mental hygiene; Dr. H. Pollack of nutrition; Dr F. D. Zeman of old age; Dr. R. W. Gerard of the functional approach to medical practice and education; Dr. R. I. Lee of physicians for the healthy; Dr. H. Emerson of the meaning of health in public health; and Dr. G. W. Larimore of "Behavior-Centered Health Education: Its Potential Contribution to the Epidemiology of Health."

It is of interest to note the deprecation of the term "positive health." Dr. Emerson writes: "Positive health is a pitiful term smacking of journalistic superfluity." That should give it its quietus.

ARTHUR S. MACNALTY.

THE CARE OF CHILDREN

Problems of Infancy and Childhood: Transactions of the Sixth Conference, March 17 and 18, 1952, New York. Edited by Professor Milton J. E. Senn, M.D. (Pp. 160. $2.50.) New York: Josiah Macy Jr. Foundation. 1953.

Would it be too much to ask all paediatricians to read this report of the sixth and last of a series of discussions arranged by the Josiah Macy Jr. Foundation? In Britain it has proved difficult to arrange discussions between those who look primarily at emotional development of infants and those who look primarily at physical development. The growth of ideas has consequently followed two disparate courses, with the result that there has been a great waste of effort and a lack of result. The statement of the developing infant as a person has been held up, and the contribution that paediatrics could make to psychiatry has been much delayed.

Taking part in these discussions were thirty members and guests, and the list of names seems to cover every branch of paediatrics—the word being used in its widest sense. The chairman is president of the International Psycho-Analytical Association. The secretary, Dr. Milton Senn, of the departments of paediatrics and psychiatry, Yale, is well known for having both a paediatric and psychological outlook. The names include Erik Erikson, author of *Childhood and Society*; the neurologist, Alan Foord; Ives Hendrick, of the Department of Psychiatry, Harvard; Benjamin Spock, author of *Baby and Child Care*; and Ernst Kris, Child Study Center, Yale.

It is impossible not to envy those who were able to be present throughout the series of discussions, the first of which is on the emotional development in the first year of life. The main contribution here is by Sibylle Escalona, and she gives the results of highly sensitive observations on the infant-mother relationship at its initiation. There is a full appreciation not only of the qualitative detail but also of the importance of all the details in the establishment of the mental health of the individual infant who is to grow eventually into an adult. The discussion brings out the various criticisms that naturally occur to those who are used to thinking in terms of physical medicine or of psychology of the kind that works on the basis of measurable quantities. Equally interesting is the discussion of the contribution by Katherine M. Wolf on the observation of individual tendencies in the first year of life. Finally, Ann Stewart gives an account of excessive crying in infants, calling this a family disease.

Only a long review could do justice to the content of these contributions. What can be done here is to invite all concerned in the care of infants to read this verbatim report.

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EXPOSURE TREATMENT OF BURNS

The local treatment of burns and scalds by means of pressure and occlusive dressings was first recorded by Koch and Allen in 1942.[1] At about the same time this method was in use in the burns unit of the Royal Infirmary, Glasgow, and it immediately became the routine practice of the large burns unit established a year later at the Accident Hospital, Birmingham. That an open wound should be covered very early and so protected from added infection is an accepted surgical principle, and the early occlusive dressing of burns was an obvious application of that principle. Soon it became clear that such dressings required initially a careful aseptic technique. If this was not provided, they could quickly change bacterial contamination to gross infection and so convert a partial to a full-thickness skin loss. For this reason cover dressings for burns became unpopular in some hospitals. It was not so much a reflection on the method as on its application.

In 1949 Wallace,[2] of Edinburgh, described the exposure treatment of burns in children. This account was followed by one from Pulaski, of the United States Army, in 1951[3] on experience with it in the treatment of more than 200 adult patients at the Brooke Army Hospital and at Tokyo Army Hospital. The treatment is based on the observation that exposure alone will allow the burned area to dry; within 48–72 hours a crust forms and will provide an efficient cover dressing. Drying is an accepted method of preventing infection, but it was further contended that "during the process of drying it is likely that an ever increasing concentration of proteins and electrolytes in the exudate exert a definite antibacterial action."[3] The method therefore seemed to offer the possibility of a self-sterilizing, self-applied cover dressing that would prevent infection and render the local treatment of burns fairly easy. Even so, Pulaski noted deaths from "overwhelming septicemia" while using this method in two patients with extensive burns (57% and 60% of body area), though it may be said at once that extensive body burns present a difficult problem in hospital care by any known method of treatment, and demand the greatest attention to every aseptic detail if infection is to be prevented.

In the Birmingham unit the exposure method of treatment has been tried alongside the closed method. Experience has shown that there is little, if any, reduction in nursing hours spent in the care of these patients by the exposure method—when they are carefully treated. Time saved in the omission of bandaging is spent on local cleanliness, the care of beds, and the prevention of deformities by immobilization of the limb in the best position of function. Ensuring that the limb is in the position of election is a time-consuming matter in all limb burns treated by the exposure method, and it is not possible to follow the method if the burn is associated with a bone or joint injury of the same limb.

Sound surface drying is indispensable to the exposure method, and when it is achieved the method has great merit. Yet sound surface drying is not always obtained. Indeed, in circumferential burns of the trunk it is not possible, for the crusts are either rubbed off or made moist by the pressure of the body against the bed in spite of repeatedly turning the patient. With burns in any situation the crust may crack and infection occur under the crust, which has then to be removed. Some burns after drying form crusts so hard and thick that they become very painful, and the pain is relieved only by their surgical removal or by their softening—thus reverting to the occlusive dressing technique.

The exposure method may be criticized in that it is expensive in hospital beds, for it is essentially an in-patient method of treatment. Further, it does not lend itself to the early transport of patients, though Pulaski claims that transport is a fairly easy matter when the crust formation is sound—after 48–72 hours' exposure in favourable cases. Again, in civilian hospital practice, particularly in large wards, women are apt to object to it even when they are covered with a large bed cradle and sheets. But it certainly has some advantages. One is that it keeps the patient cool in hot climates. And in any climate there may well be a limit to the area of the body that can be safely covered by pressure occlusive dressings. Burns of the face and perineum cannot be efficiently treated and kept clean by occlusive dressing, and undoubtedly are better treated by exposure.

No easy method or single routine has yet been discovered for the local treatment of thermal injury. In the present state of our knowledge the need for the

[1] *Surg. Gynec. Obstet.*, 1942, **74**, 914.
[2] *Brit. J. plast. Surg.*, 1949, **1**, 232.
[3] *Surgical Forum*, 1951, p. 518. Philadelphia.

establishment of some well-equipped and well-staffed burns units seems clear. It is only when thermal injuries are seen continuously and in large numbers by one unit that their main treatment problems can be recognized and solved. The aim must be to begin treatment very early, before any of the well-known complications arise, and to have sufficient staff and facilities available to do this. It is easier (and incidentally cheaper) to prevent shock, infection, and deformity than to treat these conditions when they are established.

THE BRITISH PHARMACOPOEIA, 1953

The eighth *British Pharmacopoeia*, published in March, 1953, became official on the first of this month exactly in accordance with the programme for quinquennial revision approved by the General Medical Council. Although the *Pharmacopoeia* is primarily of importance in the day-to-day work of the pharmacist and analyst, its contents have become of greater significance in medicine because of the frequency of its revision. Indeed, with the publication of a substantial *Addendum* between each full new edition and of amendments from time to time as required, the work of revision is now continuous. No longer can the *Pharmacopoeia* be said to serve as the repository of the obsolete and the obsolescent and as a closed door to the new. Successive editions may reflect changing judgments and perhaps fashions in the use of drugs, but clearly the contents are selected by critical assessment and not from sentimental attachment.

The new *Pharmacopoeia* contains 115 monographs on substances which were not official in 1948, and 130 monographs of the previous edition have been deleted. But the immediate impressions on opening the volume are the novelty of the English titles, the new arrangement of the monographs, and the clarity of the printed matter. No longer do we find "Toxinum Diphthericum Detoxicatum" but "Diphtheria Prophylactic," not "Toxinum Diphthericum Calefactum" but "Schick Control." "Oculenta—Ointments for the Eye" have become "Eye Ointments," and the names of many other preparations have been rationalized, so that, for example, the words "Aspirin Tablets" and not only "Tablets of Aspirin" now connote an official article. By the new arrangement of the monographs, preparations such as ointments, injections, or tablets follow immediately after the monograph on the active ingredient, and although this will be a convenience to doctors and analysts it will demand changes in the habits of thought of pharmacists. Some comment on the change from Latin to English titles was made at the recent British Pharmaceutical Conference, at which there was a debate between those for and those against the writing of prescriptions in English instead of Latin. Professor A. D. Macdonald said that medical and chemical specialists, in their comments on the new *Pharmacopoeia*, seemed to support English to a man. The pharmacists were about 2 to 1 in favour.

The introduction to the new *Pharmacopoeia* contains informative tables showing the rejections and selections made by the Pharmacopoeia Commission, acting no doubt in the light of views expressed by the many distinguished members of its clinical medicine and pharmacology committees and the professional and other bodies with which it consulted. Nineteen vegetable drugs and their numerous tinctures, infusions, syrups, and extracts have been deleted either because of their therapeutic inadequacies or because the active principle—for example, ergometrine—is available as a pure stable substance. All the pharmacopoeial pills and lozenges (except penicillin lozenges), the liniments of aconite and of belladonna, and some spirits and little-used injections no longer appear. Capsules and implants have been introduced as a dosage form of certain medicaments. In the list of additions the modern synthetic chemicals and the antibiotics appear most frequently. Penicillin and procaine penicillin, the streptomycins, aureomycin, and chloramphenicol, with their preparations, account for fifteen monographs not present in the 1948 edition. Among other monographs appearing for the first time are those on methadone (amidone), phenadoxone hydrochloride, globin zinc insulin, scarlet fever antitoxin and prophylactic, cyanocobalamin (vitamin B_{12}), and sodium aminosalicylate.

The Medical Act of 1950 enlarged the permitted scope of the *Pharmacopoeia* so that it can concern itself with "medicines, preparations, materials, and articles used in the practice of medicine, surgery, or midwifery." With this new freedom the Commission has added blood preparations such as human fibrin foam, human fibrinogen, dried human plasma, and human thrombin, as well as sterilized surgical catgut with standards for sterility, diameter, and tensile strength calculated on a straight pull and over a surgeon's knot. Perhaps the difficulty of turning "concentrated human red blood corpuscles" into Latin may have been a determining factor in causing the change to English titles.

The statements on dosage of the drugs show two general changes, and both might be taken with advan-

tage a step further in the next edition. The doses are expressed only in the metric system except for those substances and preparations commonly used or prescribed in the Imperial system. Thus while the dose of aspirin is stated as "0.3 to 1 g. (5 to 15 gr.)" that for stilboestrol is given in milligrams without the equivalent fractions of a grain. In most aspects of its style the *Pharmacopoeia* must be consistent, but the omission of grain doses for the sulphonamides and sex hormones and of minim doses for typhus vaccine is a commendable inconsistency. There is also a welcome tendency to expand the information on dosage and so to increase the value of the book to the prescriber. For methylthiouracil and propylthiouracil the controlling dose and the maintenance dose are now given; for sodium iodide there is a dose for the treatment of thyrotoxicosis; and information is given on the dose of picrotoxin for the treatment of barbiturate poisoning.

A leaflet on "Approved Names" issued by the General Medical Council is enclosed in each copy of the *Pharmacopoeia*, and a supplementary list of names has appeared recently. Doctors have complained that these non-proprietary names are often long and difficult to remember. Twenty years ago the introduction of a drug was something of an event, but the spate of new drugs in recent years must have caused difficulty simply from their number, apart from any system of nomenclature which might be used. Even in the past it was not unusual for long or difficult names—such as ipecacuanha, glycyrrhiza, and glycerophosphate—to be accepted. About half the approved names in the new *Pharmacopoeia* do not exceed four syllables, which seems to indicate that those responsible for selection are not unmindful of the merits of brevity. The Commission's choice is no doubt circumscribed by the need to avoid conflict with registered trade marks and, where possible, to adopt the name already in use in other countries, especially the United States, where many of the new drugs originated and received a non-proprietary name which has become familiar on the packages and in the literature. Rejection of such names as have already some currency here might cause greater confusion than the coining of yet more, though shorter, names. A long name need not necessarily be difficult, for where familiar syllables occur the name may still provide reasonable ease of pronunciation, as in nitrofurazone, hydrocortisone, and noradrenaline. But, with the prospect of the continued flow of new inventions and discoveries in materia medica, it is to be hoped that the Commission will press further in its endeavours to produce acceptable non-proprietary names.

SERVICE CAREERS INQUIRY

The serious lack of recruits to the medical branches of the armed Forces has at last forced the Government to set about making careers in them more attractive. Its proposals, which are described at page 101 of the *Supplement* this week, are in general likely to be widely welcomed by the men now serving in the Forces, and they may in the end lead to better recruitment. The Government's most important decision is to set up a "small independent committee of not more than five members" with the comprehensive task of reviewing and making recommendations on the arrangements for providing medical and dental services for the armed Forces at home and abroad in peace and war. Its chairman is to be Lord Waverley, well known as Sir John Anderson and the holder of many ministerial posts in the past, including that of Chancellor of the Exchequer in 1943–5. The names of the other members are to be announced later. The profession would wish some medical men to be included, and we may hope that the B.M.A. will be fully consulted on these appointments. The wide terms of reference given to this committee make it comparable in function to the Spens committees. It would earn the gratitude of serving medical officers if it carried out its review as thoroughly and as fairly as did those committees.

As this investigation is bound to take some time, the Government has introduced various changes to start on October 1 which, it hopes, "will result in increased numbers of medical men being attracted to make a career in the Services." These include higher pay and what are intended to be better terms of service. Rates of pay are to be raised from the middle ranks of the Services—that is, major to brigadier in the Army and equivalent ranks in the other Forces. The only information so far available on this is that the increases range from about £90 a year for a major on first appointment to about £240 a year for a brigadier. Specialist pay is to be increased, though it seems rather unlikely that the increases will be the powerful attraction that is needed. As a temporary measure a "permanent commission grant" of £1,500 (taxable) is to be paid to officers granted permanent commissions, payment being subject to the completion of one year's satisfactory service. But whether officers commissioned before October 1, and therefore not eligible for the grant, will regard it as altogether fair seems questionable. However, the results will be worth studying.

Much less can be said in favour of the decision to antedate up to seven years the seniority of late entrants to the Services. That this manœuvre will constitute a strong attraction is likely enough, and no

doubt it was fostered by the Services' desperate need for specialists. Even so, the offer is not restricted to specialists, and junior officers who entered soon after qualification will be of an uncommonly happy disposition if they do not resent seniority being given in these circumstances, sometimes to men whose first thoughts after qualifying had been far from a Service career. The fairest inducement here is surely a monetary one. But the various administrative measures intended to ease the way to a permanent commission may be helpful.

Whatever may be said of this or that inducement to join the Services, the only test must be whether it is successful in gaining and holding men in a contented Service. The Waverley committee will not have an easy task, for many of the former attractions of Service life in foreign stations have been swept away with the maps of 10 or 20 years ago. Rates of pay have become relatively more important in a world where the costs of housing and education—high enough for anyone paying his own unsubsidized way—are apt to fall with special severity on married officers. The B.M.A. already has a great deal of evidence, and will no doubt collect much more, which it is hoped may be of value to the committee. As the first thorough and independent investigation into the lot of serving medical officers for over 20 years, this promises well, and, it is to be hoped, will soon be under way.

AORTIC STENOSIS

Traditionally the diagnosis of aortic stenosis has been confined to cases showing an aortic systolic thrill, a harsh rough aortic systolic murmur, a diminished or absent aortic second sound, evidence of left ventricular hypertrophy, and an abnormal peripheral pulse (pulsus anacroticus or bisferiens). But Wiggers[1] showed that the aortic orifice must be reduced to one-quarter of its natural size before changes in the circulation can be demonstrated, and it is now widely recognized that the radial pulse and the blood pressure may be normal in patients with aortic stenosis. Evidence of left ventricular hypertrophy is also often absent. Kiloh[2] found radiological signs of enlargement of the ventricle in only two of 15 patients; only four of them showed left ventricular preponderance electrocardiographically, and the electrical axis was often vertical. The aortic second sound was normal or accentuated in 21 of the 40 patients reported by Campbell and Kauntze.[3] There remain the aortic systolic murmur and thrill, both of which signs were found in all Campbell and Kauntze's cases. White[4] regarded a systolic murmur maximal in the aortic area as almost always organic; and Willius[5] followed up patients whose aortic systolic murmur had been regarded as of no significance, and found that they all had well-marked aortic stenosis 15 to 20 years later. The diagnosis should therefore be suspected in all patients having an aortic systolic murmur, particularly if this is accompanied by a thrill. The most helpful confirmatory evidence is prominence of the ascending aorta, due to dilatation of the vessel above the stenosis, and intracardiac calcification in the neighbourhood of the aortic valves.

Rheumatic fever is generally regarded as the main cause of aortic valve disease in the first half of life and nearly always leads to aortic stenosis only after a phase of aortic regurgitation, frequently in patients who also have mitral stenosis or myocardial failure. Both Gallavardin[6] and Kiloh studied groups of patients with pure aortic stenosis under the age of 50, and concluded that they were not rheumatic. Kiloh, for example, obtained a history of rheumatic fever from 24 of 41 cases of aortic stenosis and regurgitation, but from none of his 27 patients with pure aortic stenosis. Gallavardin thought the latter group of cases might have resulted from an endocarditis of unknown type in foetal life, and drew an analogy with cases of pulmonary valvular stenosis. Campbell and Kauntze have pointed out, however, that this is now accepted as a true congenital lesion, and they think the same explanation applies to pure aortic stenosis. Kiloh thought there was no final answer to the question without necropsy evidence, but pathological studies have given rise to conflicting opinions. Karsner and Koletsky[7] found histological evidence of rheumatic infection in 196 of 200 cases of calcific aortic stenosis; Hall and Anderson,[8] on the other hand, found microscopic rheumatic lesions in all but eight of 112 hearts which showed no gross valvular disease, and concluded that such evidence is of no value in the pathological diagnosis of a valvular lesion.

It seems reasonable to conclude with Campbell and Kauntze that at present the aetiology of aortic valvular stenosis may be more accurately assessed from the history, progress, and physical signs than from necropsy material; and that the weight of evidence favours congenital malformation as a common cause, even in patients not diagnosed until adult life.

1 *Physiology in Health and Disease*. London. 1935.
2 *Brit. Heart J.*, 1950, **12**, 33.
3 Ibid., 1953, **15**, 179.
4 *Heart Disease*. New York. 1944.
5 *Proc. Mayo Clin.*, 1939, **14**, 671.
6 *J. Méd. Lyon*, 1936, **17**, 593.
7 *Calcific Disease of the Aortic Valve*. Philadelphia. 1947.
8 *Amer. J. Path.*, 1942, **18**, 778.

YOUNG'S SYNDROME

Since anterior pituitary growth hormone is diabetogenic in adult animals under some conditions[1] the frequent association of acromegaly and diabetes mellitus is understandable. But whether diabetes mellitus ever occurs as a result of the over-secretion of growth hormone otherwise than in acromegaly has been a matter for debate during the past few years.

In the Sydney Ringer Memorial Lecture for 1950 published in these columns[2] Professor F. G. Young argued that "in the human being a slightly excessive rate of secretion of growth hormone, insufficient to cause overt signs of acromegaly but lasting a long time, might lead to a prolonged but not excessive restraint upon the processes of carbohydrate and protein catabolism and oxidation, combined with the increase in appetite

1 Cotes, P. M., Reid, E., and Young, F. G., *Nature (Lond.)*, 1949, **164**, 209.
2 Young, F. G., *British Medical Journal*, 1951, **2**, 1167.
3 —— *Recent Progr. Hormone Res.*, 1953, **8**, 471.
4 *Presse méd.*, 1953, **61**, 495.

characteristic of growth hormone activity, so that diabetes ultimately develops." In the same lecture Young surveyed the metabolic influences of growth hormone other than that of stimulating growth, a subject he has discussed more recently[3] in greater detail with respect to diabetes.

The actions of growth hormone discussed by Young which might be observed clinically include an augmented secretion of milk, seen in the cow in declining lactation, and the production of abnormally large offspring, observed in the rat. Although the accidents of pregnancy observed in diabetic women who produce large babies might be related to oversecretion of growth hormone, Young is inclined to ascribe these to factors other than the action of growth hormone.[2] The possibility that growth hormone is responsible for the excessive weight of diabetic patients, and even adiposity, has also seriously to be considered.[2]

Recently Abaza, Varron-Vial, and Rombauts have described[4] a condition in women, called by them the "syndrome de Young," which is associated with prolonged growth, high foetal or neonatal mortality, large babies, hyperlactation, obesity, and diabetes. They describe two complete cases of this syndrome, which they have studied over a long period of time, and state that, although the complete syndrome is rare, fragments of it are more often seen. They ascribe the first association of these symptoms to Young's experimental work on pituitary diabetes, and refer in particular to the Ringer Memorial Lecture.

As the authors say, the recognition of this syndrome is of great interest both clinically and theoretically. If in fact a slight hypersecretion of growth hormone can be associated with metabolic changes but unaccompanied by the obvious stigmata of acromegaly, then a wide field of clinical investigation may await exploration. It may be that the grotesque conditions ascribed classically to endocrine hypersecretion represent only the extreme and obvious result of a disturbance of function which may be seen in more subtle and perhaps qualitatively different aspects. So far the French physicians have observed only two instances of "Young's syndrome." It will be of great interest to know whether doctors in Britain and in the U.S.A. are able to extend these observations and confirm the bizarre association of symptoms foreshadowed on a purely experimental basis.

POLIOMYELITIS AND INOCULATIONS

The literature on the relation between inoculations and poliomyelitis continues to grow. A few weeks ago in this *Journal* Dr. J. Grant[1] reviewed his experience in the Gateshead district in 1952, which was similar in many respects to that recorded by other authors.[2-6] In another recent paper Geffen, Paterson, and Tracey[7] have reported on the condition of 29 children who two years previously had developed poliomyelitis after having received inoculations. They concluded that, although paralysis after recent inoculation appeared to be relatively limited in extent, the paralysis in the inoculated limb was nearly always severe. Recovery of a limb depended on the initial severity of the paralysis, whether or not it had been inoculated.

Our present comparative freedom from diphtheria is due to the high level of artificial immunity in the community, and those who now enjoy the fruits of the diphtheria immunization campaign have a responsibility to maintain the immunity of the child population. At the same time the prevention of paralysis during outbreaks of poliomyelitis is of great importance, and ways of reconciling the duty of protecting children against diphtheria and other diseases with that of preventing paralysis are being sought, with good prospects of success. Bousfield[8 9] sees the answer to this question in the use of a non-irritant purified fluid formol toxoid given by the subcutaneous route. This recommendation is based on reasonable assumptions, but it is too early yet to say that such methods of immunization are completely free from the risk of paralysis. A statement by the American Public Health Service[10] describes diphtheria, tetanus, and whooping-cough as serious diseases which unchecked present a far greater hazard than poliomyelitis. It states that the risk of post-inoculation poliomyelitis can be avoided by carrying out immunizations when poliomyelitis is not epidemic in the community, but that there is no good reason for withholding immunization during the summer months in communities that are not having an epidemic of poliomyelitis. And it recommends that, as the danger of whooping-cough is so great in infants under the age of 6 months, immunization procedures should be continued in these young children even through an epidemic of poliomyelitis.

The Ministry of Health[11] has suggested that "until our knowledge is more precise it will be wise to suspend immunization when poliomyelitis is prevalent in any district." But a report of the World Health Organization[12] states that practice might be different in serious and minor epidemics. While recommending the suspension of all immunization when the disease assumes serious epidemic proportions in any given area, the report advises that when the epidemic is of minor severity immunization with diphtheria and whooping-cough vaccines should be continued, but the use of the adsorbed combined vaccine should be discouraged.

The decision to cease immunization in an area carries with it an immediate obligation to make plans for overtaking arrears when the time is suitable, and the timing of immunization publicity campaigns must be adjusted accordingly.

Dr. E. D. Adrian, O.M., P.R.S., Master of Trinity College, Cambridge, has been elected President of the British Association for 1954. The only other Presidents of the British Association who have also been Presidents of the Royal Society at the same time were Lord Lister in 1896, Sir Charles Sherrington in 1922, and Sir Frederick Gowland Hopkins in 1933, all three medical men like Dr. Adrian.

1 *British Medical Journal*, 1953, **2**, 66.
2 Geffen, D. H., *Med. Offr*, 1950, **83**, 137.
3 Martin, J. K., *Arch. Dis. Childh.*, 1950, **25**, 1.
4 McCloskey, B. P., *Lancet*, 1950, **1**, 659.
5 Bradford Hill, A., and Knowelden, J., *British Medical Journal*, 1950, **2**, 1.
6 Korns, R. F., Albrecht, R. M., and Locke, F. B., *Amer. J. publ. Hlth*, 1952, **42**, 153.
7 *Lancet*, 1953, **1**, 1268.
8 Ibid., 1953, **2**, 43.
9 *British Medical Journal*, 1953, **2**, 285.
10 *Publ. Hlth Rep. (Wash.)*, 1952, **67**, 495.
11 *A. R. Med. Offr. Minist. Hlth. Lond.*, 1951, 30
12 *W.H.O. Tech. Rep. Ser. No.* 61, 1953, 40.

BRITISH ASSOCIATION

The 115th annual meeting of the British Association for the Advancement of Science was held at Liverpool from September 2 to 9 under the presidency of Sir EDWARD APPLETON, F.R.S. Sir Edward in his address spoke on "Science for its Own Sake," using as an illustration the still-developing field of radio-astronomy.

Interest was aroused by the inclusion by Professor G. R. CLEMO, F.R.S. (Chemistry Department, King's College, Newcastle-upon-Tyne), in his presidential address to the Section of Chemistry, of a preliminary statement on the analysis of solid material collected from city smoke on filters used to clean the air supply to his department. Several grammes weight of material have been obtained and the first isolations of pure organic substances from smoke are in progress. The evidence thus far is consistent with the presence of several pyrene derivatives, including benzpyrene.*

Carotenoids

The Section of Physiology opened its programme with a symposium on the carotenoids, a class of pigments described by Professor R. A. MORTON, F.R.S. (Department of Biochemistry, Liverpool University), as excelled in physiological interest only perhaps by the porphyrins. He defined the problems now occupying the stage as their biogenesis, function in plants and animals, and conservation in animal feeding-stuffs.

Work on biogenesis has been done on a small fungus, *Phycomyces blakesleeanus*, on tomatoes, and on a photosynthetic bacterium, *Rhodospirillum rubrum*. It was summarized by Dr. T. W. GOODWIN (Department of Biochemistry, Liverpool University). Leucine is thought to provide the basic 5-carbon unit from which, after several intermediate steps, the 40-carbon carotenoids are built up, probably by more than one route even in a single species.

Sex differences in the distribution of the carotenoids were discussed by Dr. THOMAS MOORE (Dunn Nutritional Laboratory, Cambridge). There are many instances in plants and the simpler animals. There is carotene in the male but not in the female organs of certain seaweeds; the male starfish is three times richer in carotenoids than is the female. In human beings, there is more vitamin A (of which β-carotene is the precursor) in the blood of a man, and more carotene in the blood of a woman. There are also differences in the mode of storage of the vitamin, this being mainly in the liver of a woman, but in men in the kidneys. In diabetic subjects there are changes in the distribution of vitamin A and carotene in the directions found normally in women, who show also the higher incidence of the disease.

Dr. H. J. A. DARTNALL (Medical Research Council, Vision Research Unit) spoke on the light-sensitive substances of vision. The chief problem of human physiology is that, whereas a total of six visual pigments are known from different species of animals, only visual purple, of which the absorption spectrum corresponds with the sensitivity of dark-adapted vision, has been obtained from the human retina. The absence of further pigments associated with light-adapted, and therefore with colour, vision may be explained by recent work which suggests that the most commonly used extractive, digitonin, may destroy these chemically more fragile visual pigments.

Physiology of Athletic Training

In a discussion on the physiology of athletic training both Professor A. HEMINGWAY (Department of Physiology, Leeds University) and Mr. R. G. BANNISTER (St. Mary's Hospital Medical School, London) sought to relate the severe training schedules followed by long-distance runners with physiological effects. Professor Hemingway thought that almost certainly there was a contribution to improved performance by increasing the reserve of the heart—the ability to increase both heart rate and the volume of blood expelled per beat, particularly the latter. He saw a connexion also between the avoidance of tenseness, which probably was important, and the efficient performance of the heart. Mr. Bannister described treadmill experiments with subjects breathing different proportions of oxygen. He thought they could be explained only in terms of a reduced oxygen-saturation of arterial blood during exercise. He suggested that rigorous training was, in effect, an alternative to enriching the inspired air with oxygen. The greatest scope for athletic improvement lay in the distance events.

Nutrition in Man and Ruminants

Comparisons between the nutrition of man and ruminants were made in the presidential address to the Section of Physiology by Dr. D. P. CUTHBERTSON (Director, Rowett Research Institute, Bucksburn) and in a symposium held later with the Section of Agriculture. In relation to ruminants Dr. Cuthbertson pointed out that the degradation as well as the synthesis of protein by rumen micro-organisms had to be considered, and recalled that casein supplements fed to hill ewes on a low plane of nutrition were used very inefficiently despite the animals' need for protein. Of human dietary preferences, he stated that it looked as if the composition (protein proportion) of the food consumed to meet energy needs had tended to be so adjusted as to meet maximal demands for growth and reproduction, any other natural arrangement being unlikely to survive. Mr. R. J. GARNER (Lecturer in Chemical Pathology, Bristol University) thought that the adaptation of the adult ruminant to a low level of blood sugar might be partly explained by the need to conserve glucose for essential functions.

Professor J. W. HOWIE (Department of Bacteriology, Glasgow University) summarized recent evidence on the relation between diet and resistance to infection. On the one hand, it had been shown from 1944 onwards that resistance to a number of virus infections was increased by a diet which was less adequate for the host, and during the past two years that increased resistance to certain protozoal infections was conferred on rats, monkeys, and mice by a diet of milk and milk casein. On the other hand, there was evidence that more antitoxin is produced in well-nourished animals in response to artificial immunization—and faith in this respect had been justified.

Natural History of Disease

A final symposium on the natural history of certain communicable diseases was opened by Professor B. G. MAEGRAITH (Department of Tropical Medicine, Liverpool University). He stated that, while ultimate pathological patterns had been closely studied, local and general processes involved in the production of injury to the host had been largely neglected until lately, and the reaction of the host on the parasite had been neglected also. The balance, host–parasite–host, was such that in many ways better results might follow the study of an infective agent in its natural host—for example, filariasis in the cotton rat—than by the study of an agent artificially supported in an unnatural host—for example, the trypanosomes of sleeping sickness cultured in mouse or rat. Professor R. M. GORDON (Department of Entomology and Parasitology, Liverpool University) and Dr. R. B. GRIFFITHS (Department of Tropical Medicine) discussed the classification of filarial species on the basis that those producing violent reactions in their hosts were ill-adapted to them, and vice versa. In the case of the pathological organism *Loa loa* there was some evidence for the existence of a better-adapted host. Dr. W. H. H. ANDREWS (Department of Tropical Medicine, Liverpool University) described research on the blood supply to the liver—the experimental approach being to provide a background for the study of malaria. The special blood supply reported to serve the central zone of the liver did not appear to exist, and this zone was the most vulnerable to anoxia. Dr. K. R. DUMBELL (Department of Bacteriology, Liverpool University), speaking also for Professor A. W. Downie and Dr. K. McCarthy, followed a discussion of the varying severity of symptoms found in a number of virus diseases with the speculation, "fascinating to the research worker," of so modifying a virus as to be relatively harmless to its host—although immunization remained the best chance

* Spectroscopic determinations of benzpyrene in city air have been previously reported by R. E. Waller, *Brit. J. Cancer*, 1952, 6, 8; see also Doll, R., *British Medical Journal*, 1953, 2, 521 and 585.

of protection. Professor T. H. DAVEY (Department of Tropical Hygiene, Liverpool University) developed the argument that measures for increased food production in underdeveloped countries should be effected at the same time as public health schemes, and, since they take longer to mature, they should, in general, begin first.

Computing Machines and Biological Theory

Professor L. ROSENHEAD, F.R.S. (Department of Applied Mathematics, Liverpool University), spoke of the revolution in theoretical science which might be expected from the proper use of electronic computing machines. Whereas many of the variables found in nature were customarily omitted in the interests of simplicity, a new approach could now be made without the necessity for such restriction. Among the sciences likely to be affected he listed specifically biology and theoretical chemistry—and he suggested that the effects would be more far-reaching in the long run than those of splitting the atom. Knowledge of the central nervous system might gain more from ability to compute, he suggested, than from the drawing of analogies with computing machines. None the less, a discussion on "cybernetics" was held jointly by the Sections of Psychology, Mathematics, Physics, and Physiology—with the emphasis rather on the need for a proper discipline in such analogies.

EIGHTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

[BY A SPECIAL CORRESPONDENT]

The proceedings of the Eighth International Congress on Rheumatic Diseases in Geneva last month serve to measure the advances made in rheumatology since the last congress, which was held in New York four years ago. At that meeting Hench first announced the success of cortisone and A.C.T.H. in the treatment of rheumatoid arthritis. This time attention was concentrated on three main themes: the progress made in the hormone therapy of the collagen group of diseases; the pharmacology of the various drugs used in treating rheumatic patients; and the rehabilitation of the crippled arthritic. In the first of these fields, if little has yet been discovered about the basic physiology of the steroid hormones, a good deal has been learned of their therapeutic potentialities and of the proper technique of their use. The opening paper contributed by Hench himself brilliantly summarized the present status of hormone therapy in the rheumatic field. He felt that the selection of cases for cortisone treatment must be made more critically and the technique of dosage considerably modified. Subject to these considerations, however, he thought cortisone was the most useful adjunct to established therapy in many kinds of rheumatoid arthritis, and the method of choice in some. Above other considerations, however, he stressed the continuing value of the steroid hormones as research tools for the further study of both the rheumatic and certain other groups of diseases.

"Electrocortin"

Cortisone has never been considered the *ne plus ultra* of endocrine treatment. Even in 1949 Hench described its discovery as being not the beginning of the end but the end of the beginning of successful therapy. It was therefore with considerable excitement that the delegates heard Professor T. Reichstein, the Nobel Laureate, announce the isolation in pure crystalline form of a new steroid hormone derived from the amorphous fraction of the adrenal cortex (*Journal*, September 5, p. 552). This hormone has been provisionally named "electrocortin" by the English workers Simpson and Tait, since it appears to be principally concerned with the mineralo-corticoid processes of body metabolism. It is possible that the new hormone may prove able to counteract some of the side-effects which at present complicate cortisone and A.C.T.H. therapy. At present no more than 22 mg. has been prepared, but as the process of extraction is simplified no doubt much more will be heard of this work and its implications in physiology and medicine.

Many practitioners who originally espoused the cause of hormone therapy in the rheumatic field with somewhat uncritical enthusiasm experienced a revulsion of feeling when it became evident that the technique was far from foolproof. The recent upsurge of interest in new and powerful analgesic drugs of the phenylbutazone group is probably a measure of this feeling of disillusionment. As was to be expected in the home of "butazolidin," much time was devoted to discussion of its virtues and vices.

The Crippled Housewife

The third major theme of the Congress concerned the application of modern methods of rehabilitation to the special problems of the rheumatoid arthritic cripple. Rusk and others pointed out that Government-sponsored schemes of sheltered employment constitute no solution to this problem, since the vast majority of the victims of this disease are housewives, outside the scope of such methods. The need for a new technique of rehabilitation in the home environment presents a challenge to the medical profession.

Nova et Vetera

EXECUTED FOR TREASON

Dr. Archibald Cameron, the Jacobite physician, was executed 200 years ago for high treason. He was the last victim of the 1745 and the last person to suffer death by Act of Attainder in this country.

Dr. Cameron was the brother of Donald Cameron of Lochiel, head of the Cameron clan. Donald raised a band of 1,200 for the service of the Young Pretender in 1745. He persuaded Archibald to be in medical charge of these men. The doctor agreed to this with reluctance, but refused to accept a commission.

When the battle of Culloden put an end to the rebellion and the hopes of the Young Pretender, he together with Lochiel and Archibald Cameron and others embarked from Flotta, in the isle of South Uist, and landed in France at Boulogne after enduring very severe hardships.

The doctor visited Scotland four years later, to obtain assistance for himself and his fellow sufferers abroad. He returned to France, and in 1753 he again came to England. The Government heard of this and sent troops to arrest him. By following a small boy who it was believed had knowledge of the whereabouts of the doctor, they were able to trace his hiding-place. He was arrested and taken to the Tower. When brought before the King's Bench for trial, as he was one of those mentioned in the Act of Attainder passed after the 1745 rebellion for the effectual punishment of those concerned in it, the Crown demanded that Cameron should be at once sentenced to death without trial. The Act mentioned a large number of names, including Dr. Cameron, and stated that any of them who did not submit to justice before July, 1746, was attaint of high treason.

The Crown's wish to dispense with a trial was refused, and he pleaded he had a claim on the mercy of the court. He had been unwilling but over-persuaded to join the forces of the clan, and he had attended wounded on both sides impartially. He threw himself on His Majesty's clemency.

The Lord Chief Justice pronounced sentence as follows:

"You Archibald Cameron of Lochiel, in that part of Great Britain called Scotland, must be removed from hence to His Majesty's prison of the Tower of London and on Tuesday, the seventh of June next your body to be drawn on a sledge to the place of execution, there to be hanged but not till you are dead, your bowels to be taken out, your body quartered, your head to be cut off and affixed at the King's pleasure, and the Lord have mercy on your soul."

On June 7, 1753, at about 10 a.m. he was brought from the Tower, escorted by a party of horse guards. Put on a hurdle and fastened to it by the executioner, he was drawn through

the City to Tyburn and there helped into the cart. The method of execution at that time was to put the person in a cart, tie a rope round his neck, attach the rope to a beam, and then drive the cart away, leaving the victim to die of strangulation. Dr. Cameron begged the sheriff to allow his body to hang till he was dead, and the officer said he would do this. The body was allowed to hang for 45 minutes. Then the executioner cut off his head, removed the bowels, but did not quarter the body.

At this distance of time, when it is possible to review the case dispassionately, the execution of this doctor, eight years after the rebellion was over, appears to have been a cruel and vindictive proceeding, especially in view of the small and unwilling part he took in the rising.

L. A. PARRY.

Preparations and Appliances

A DISPOSABLE OXYGEN MASK

Dr. T. H. S. BURNS and Dr. J. M. HALL, of the Department of Anaesthetics, Guy's Hospital, write: We have recently been presented by the British Oxygen Company with some disposable oxygen masks which appear to have certain advantages over other methods of oxygen therapy.

The mask is of polyvinyl chloride and is divided into two compartments, of which the outer is the larger. These communicate with each other through two holes 12 mm. in diameter. Oxygen is fed into the larger compartment and is drawn through the large holes by the patient's inspiration. Expiration takes place chiefly through two holes 6 mm. in diameter which connect the smaller compartment with the surrounding atmosphere. When the patient inspires, some air is drawn through these holes. However, provided that oxygen is entering the mask at about 8 litres a minute, and the patient is not grossly hyperventilating, this diluting effect is small. A malleable metal strip is incorporated into the rim of the mask to facilitate its adaptation to the contour of the face. The mask is kept in position by means of a simple elastic "harness," which is slipped over the back of the wearer's head. Fig. 1 shows the mask in position.

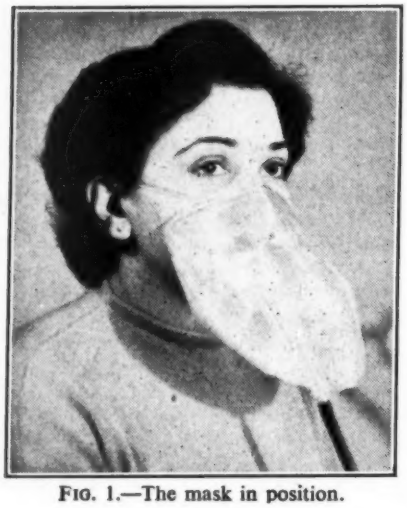


FIG. 1.—The mask in position.

METHOD

Throughout the tests oxygen was delivered to the masks at a steady rate of 8 litres a minute. The average number of respirations per minute was 12, with a tidal volume of 650 ml. The oxygen percentage in alveolar air was measured at 0, ¼, 1, 2, 5, 15, and 30 minutes.

Samples of alveolar air were obtained by the technique described by Grollman and Marshall (1928). They showed that if a person rebreathes into a 2.5-litre bag six or seven times in 15 seconds the mixture in the bag is in equilibrium with that in the lungs. The gas percentages in the mixture are not influenced by rebreathing, since the manœuvre is carried out in less than the circulation time. Samples of alveolar air taken in this way were measured with the aid of the British Oxygen Company oxygen analyser.

Fig. 2 shows that the alveolar oxygen percentage increases rapidly for one minute, reaching 56–60% in that time. Continued breathing of oxygen at 8 litres a minute does not cause any further significant rise in this figure.

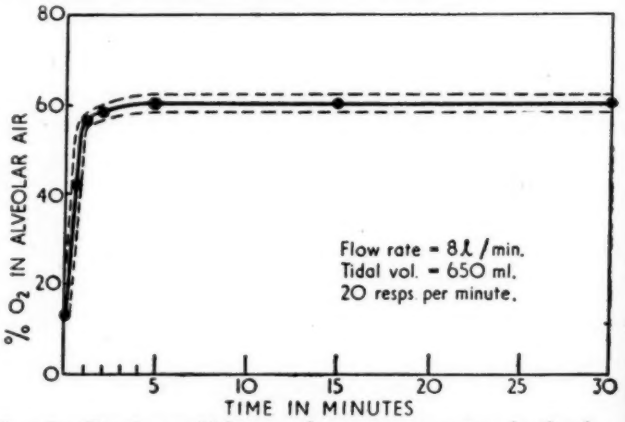


FIG. 2.—Showing rapid increase in oxygen percentage in alveolar air.

Since no valves cover the holes in the mask, it was felt that gross overbreathing on the part of the patient might result in the oxygen mixture's being considerably diluted with air drawn in through the expiratory holes. The effect of this was tested as follows.

One of us (T. H. S. B.) breathed four times a minute with a tidal volume of 5 litres. After three minutes and after five minutes of this type of respiration the average alveolar oxygen percentage was found to be 38–44. In other words, with normal use alveolar oxygen percentage rises to 60 in one minute. Gross hyperventilation of an order not to be expected in clinical practice will only reduce this to 40%, which is nearly three times the normal alveolar oxygen percentage.

USES

This mask appears to be very suitable for any patients requiring not more than 60% oxygen in alveolar air. It is comfortable to wear and there is no unpleasant smell. It is easy to fit on a patient, and remains airtight without difficulty. However, it would have to be removed for eating or drinking.

A type of mask such as the Haldane or B.L.B. will give a higher concentration of oxygen in a co-operative patient and would seem to be more suitable for long-term administration. The disposable mask seems most useful for patients who are unconscious or uncooperative—for example, those returning from the theatre to the ward or during the immediate post-operative period. Here it is desirable to attain a high oxygen concentration quickly. It is difficult to keep a B.L.B. mask airtight on an unconscious patient, and the disposable mask attains a higher oxygen concentration in one minute than an oxygen tent obtains in half an hour for equivalent flow rates of oxygen.

The only technical difficulties which we encountered with this mask were: (1) It is so light that even the weight of a small rubber tube leading to the mask from the oxygen supply can kink the mask. This does not prevent the flow of oxygen significantly, but it gives rise to a disturbing noise. It is understood that this feature is having attention from the manufacturers. (2) Some care is necessary in fitting the mask on unconscious patients. The chin should be inserted into the mask first and then the malleable metal strip manipulated over the nose.

These masks cannot easily be sterilized, but as a price in the region of 1s. each has been quoted it would seem reasonable to use them for one patient only.

We are indebted to the British Oxygen Company, Research and Development Division, for the loan of the oxygen analyser, and to Miss M. J. Waldron, of Guy's Hospital Illustration Department, for the drawing.

REFERENCE

Grollman, A., and Marshall, E. K., jun. (1928). *Amer. J. Physiol.*, **86**, 110.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

The Cultured Student

SIR,—The public addresses of Sir Lionel Whitby and Sir Richard Livingstone at the First World Conference on Medical Education (*Journal*, August 29, pp. 451 and 454) have been received with very high appreciation, and the Council of this Guild has asked us to thank them for the devotion and preparation that this has implied and to thank you also for your speedy and full publication.

Sir Lionel has said that an education which ignores the humanities is disastrously incomplete. We have been asked to express the hope that the deans of our great medical schools will not only note the published statement that there is now some poverty of mind in the new medical and science graduates, but that they will pledge themselves, with the assistance of their academic boards, to take the necessary practical steps that will maintain the character of the sons of Hippocrates, and that the vague slogan of "the philosophy of the first-rate" will be interpreted as a necessary course in reasoned medical ethics.—We are, etc.,

W. B. J. PEMBERTON,
Master.
W. J. O'DONOVAN,
Hon. Secretary.
London, W.1. Guild of St. Luke, SS. Cosmas and Damian.

SIR,—The season of mists and mellow fruitfulness is the season also, by developing custom, when the elder brethren of the profession take it upon themselves to remind the medical student and his newly qualified colleague of their deplorably uneducated status in the arts and humanities. The opening that presented itself this year in the World Conference on Medical Education has been handsomely taken advantage of, and the accused should now know, without any manner or shadow of doubt, just how low they grade in the cultural scale.

It is no doubt true that few of them could distinguish a Boucher from a Botticelli, quote a stanza from the *Ode to a Nightingale*, or tell who imprisoned Montezuma and who strangled Atahualpa—facts which, according to Macaulay, every schoolboy in his day knew. I am sure also that the annual castigation is carried out more in sorrow than from any sense of superiority, but, it seems to me, with a certain blindness to the actualities of the relevant situation. Stephen Leacock remarked: "An education, when it is all written out on foolscap, covers nearly 10 sheets. It takes about six years of severe college training to acquire it. Even then a man often finds that he somehow hasn't got his education just where he can put his thumb on it."

It is, perhaps unfortunately, very advisable these days for the young graduate with ambition to have his medical education where he can put his thumb on it whenever necessary. He will no doubt have heard that "Art is long and Time is fleeting," and reality will have impressed on him the remainder of the stanza that our hearts, though stout and brave, still like muffled drums are beating funeral marches to the grave. Consequently, in the fiercer competition which exists to-day for the better posts in medicine the young doctor can be forgiven if he concentrates on the studies which will promote his advancement in his profession, even if it means foregoing the pleasure of being able to discuss the transcendentalism of Kant with his N.H.S. patients.

May I suggest a truce to these sermons, which I cannot help thinking are slightly tinged with humbug? Sir Sydney Smith remarks in the course of a valedictory address[1] to the newly qualified that if it is true, as is sometimes said, that only the study of the literature written in the Greek and Latin tongues can produce "that ennobling and beautifying effect on the mind," he has failed to notice it in his classical colleagues. If and when they hear of committees appointing candidates to the higher positions in the profession out of admiration for their general culture, young graduates may be expected to take the annual objurgations seriously. But it is a point worth bearing in mind that when these untutored fledglings begin to turn their thoughts to the arts it may be the literary incomprehensibles, contrapuntal *brouhahas* and teratological chiaroscuro, the pride of contemporary art, which will be preferred. You will, I trust, agree, Sir, a most horrid possibility.—I am, etc.,

London, W.C.1. FREDERICK DILLON.

REFERENCE

[1] *Lancet*, 1953, 2, 461.

Blood Transfusion Accidents

SIR,—Your letter from Dr. George Discombe (*Journal*, September 5, p. 569) no doubt reflects the regrets of many clinical pathologists on reading the "statement" published by you from the Consulting Pathologists Group Committee (*Journal*, August 15, p. 390). It reflects my regrets even more, as it was published in advance of a discussion to be held at the end of September by the Group on this problem, and so can hardly claim to be a statement of representative thought.

Dr. Discombe is surely right in reiterating the value of the Coombs test.

The Committee favours a tie-on label ("a good arrangement") for use when labelling cross-matched blood. In other words the members favour the issuing of a bottle of blood with a label that is removed during the actual transfusion, a dangerous practice. Have a tie-on label by all means—the NBTS (National Blood Transfusion Service) 11 label is excellent. In addition a gummed label stuck on to the bottle by the person carrying out the cross-matching, with patient's name, etc., and cross-matcher's signature and date, should surely never be omitted. The label NBTS 10 is provided already gummed for this, and NBTS 9 for packed cells.—I am, etc.,

Macclesfield. C. A. K. BIRD.

SIR,—Dr. George Discombe's letter (*Journal*, September 5, p. 569) raises a question which has interested me for some years—who has decided that the tube method of grouping is more reliable than the tile, and on what grounds? Could it be that the tile method has been condemned because more transfusion accidents have occurred in hospitals where the tile method is used than in those where the tube method is employed? Surely not. No one knows what percentage of laboratories up and down the country use the tile as opposed to the tube, but it would be my guess that some 90% use the tile.

I have used, and taught the use of, the tile method with suitable technique and suitable precautions for over a quarter of a century. So far I have not been involved in an untoward number of mismatched ABO transfusions. I hesitate to court disaster by saying that the number is precisely nil.—I am, etc.,

Guildford. C. RICKWORD LANE.

SIR,—The safety factor in any blood-grouping technique is a function of the technician carrying out the tests rather than of the particular method used. Thus, tile ABO grouping and even the Chown Rh grouping technique in the hands of a really experienced worker are probably safer than tube grouping by a relatively inexperienced medical officer or technician. It would, I feel, be wrong for any authority to do more than recommend techniques; but this should not prevent them offering advice or suggesting procedures which had not only stood the test of time in specialist laboratories, but which also present the best possible answer to any claim arising out of mis-matching accidents and possible litigation which is all too common nowadays. Similarly, it is surely unwise for any individual

pathologist to advocate for general use techniques which, although suitable for his own laboratory and within the scope of the facilities at his disposal, may be quite impracticable and even dangerous for other institutions less well equipped.

Dr. George Discombe (*Journal*, September 5, p. 569) does less than justice to the Consulting Pathologists Group Committee (*Journal*, August 15, p. 390). This Group is doing a service to the whole profession by ventilating the necessity for greater care and expert supervision in all stages of blood transfusion. It is particularly gratifying to note the Committee's reference to over-prescribing and to its plea for closer co-operation between clinicians and pathologists in this important field.

There is no doubt in the minds of most workers that a full two-hour tube technique for both ABO and Rh grouping is essential to confer the maximum safety: but both the Consulting Pathologists Group Committee and Dr. Discombe, and indeed all blood-groupers, realize the necessity for a speedier technique in emergency cases. It is certain that emergency transfusions carry a higher accident rate than do the routine "cold" cases, mainly because of the inexperience of available groupers (these cases frequently occur outside laboratory hours), who confuse their readings with anti-A and anti-B sera. There is indeed a popular "Medical Aid" in which the readings with these two sera are reversed, and were its instructions carried out an incompatible transfusion would certainly result.

This confusion with anti-A and anti-B is much commoner than is generally supposed. In his article on incompatible transfusion[1] Dr. Discombe quotes the case histories of 12 patients, and in no fewer than 8 of these there would appear to be a group B complication.

The solution of the emergency transfusion would be simple if group O Rh-negative blood were in unlimited supply; but this group must always be relatively scarce because of its use in true emergencies and in babies with haemolytic disease. There is, however, a middle course alternative to the full two-hour grouping and the indiscriminate use of group O Rh-negative blood. This is to make use of both groups O and A Rh-negative by a simplified means of testing which avoids completely the use of anti-B serum. This will be described in detail in the near future.

Short-cuts to full tube grouping and cross-matching are innumerable; but these should be reserved for real emergency cases. Good organization and better co-operation between clinicians and pathologists can do much to reduce the number of so-called emergencies. When a short-cut is adopted it should be realized that an increased risk is involved. If the case is really an emergency the extra risk can be easily justified; but often the alleged emergency arises out of bad organization and lack of co-operation, as Dr. Discombe states.

There is certainly a great deal to be said for the consultant pathologist being provided with greater authority and better accommodation and staff in order to supervise properly all aspects of blood grouping, cross-matching, and the subsequent blood transfusion. There are still too many hospitals where the decision to transfuse and the grouping and cross-matching of blood devolve upon the most junior medical staff with corresponding disastrous results.—I am, etc.,

R. A. ZEITLIN.

South London Blood Transfusion Centre, Sutton.

REFERENCE

[1] *Lancet*, 1952, **1**, 734.

The Pain of Transurethral Manipulations

SIR,—Dr. E. C. Atkinson rightly draws attention to the ordeal of male urethral instrumentation without proper anaesthesia (*Journal*, August 22, p. 440). To-day, when the modern improved surface anaesthetic is available, there is no justification for the omission of it and no need for failure or partial failure of local analgesia.

One or two helpful points in technique may be worth mentioning again in these columns. The effectiveness of local analgesia of the posterior urethra may be ensured by using a ball-ended needle originally designed for the retrograde injection of the saphenous vein.[1] The small ball end is smeared with anaesthetic lubricant and passed down to the posterior urethra without discomfort. Two to three ml. of surface anaesthetic solution is injected slowly, followed by 5 ml. of the solution made up as a lubricant. A wet swab is then tied lightly round the penis with a half knot and left *in situ* for 10 minutes.

Although skill in passing the instrument is of first importance to the medical mind and may even be considered adequate in itself, the wide range of variation in the patient's sensoria and in the local state of the urethra is strong argument for the kind supplement of effective local analgesia in every case.—I am, etc.,

London, E.11. D. LANG STEVENSON.

REFERENCE

[1] *Lancet*, 1938, **1**, 27.

SIR,—Dr. E. C. Atkinson's letter (*Journal*, August 22, p. 440) prompts me to record my personal experience. There is undoubtedly a highly efficient and safe local analgesic for the urethra; it is one that I have used on several thousand occasions without mishap. So far as I know it was introduced into London by the late Canny Ryall, and I should be surprised to learn that those of his colleagues who worked with him and are still in practice do not continue to employ it. It is a weak solution of cocaine hydrochloride. A 3-gr. (0.2-g.) powder of cocaine hydrochloride is added to 1¼ oz. (36 ml.) of a solution consisting of ½% sodium bicarbonate and ½% chlorbutol.

I have always maintained the routine of making the solution up freshly for each instrumentation. It is then instilled into the urethra and retained there with a penile clamp for five minutes.

Whether the details I have described vary from Canny Ryall's original ones I do not know, but I can strongly recommend the analgesic used in this way. In the past there has been a prejudice against employing cocaine in the urethra, mostly because it seems to have been used in proportions which are dangerous.—I am, etc.,

London, W.1. H. P. WINSBURY-WHITE.

Breast-feeding

SIR,—I have read with interest the latest report on the Oxford child health survey (Drs. Alice Stewart and Celia Westropp, *Journal*, August 8, p. 305) and the ensuing correspondence. It is surprising to me that no one has so far queried the use of incidence or attack rates as a measure of ill-health. My own advocacy of breast-feeding arose in the first place from observation of children in general practice; and what the G.P. is in a position to observe is the different resilience of different children. This is so striking that I have gradually come to think of health in children not in terms of what they catch but of how they get over it.

In respect of most complaints there is little reason to expect the incidence to vary much from group to group. It depends (as is confirmed by the Oxford figures on colds) on environmental factors, which the mode of feeding does not affect. The complication and recovery rates should differ much more than the attack rates.

No doubt it is now impossible to obtain any measure of the length of the illness recorded in the Oxford survey. In any current survey, the measurement of length of illness through such an index as the number of doctor's visits presents statistical difficulties. They are not insurmountable, however; and I feel that while this feature of the picture is left out there is no real measurement of morbidity.—I am, etc.,

York. F. CHARLOTTE NAISH.

Hat-pin Haemoptysis

SIR,—Subcutaneous emphysema is not an uncommon condition, having a variety of possible causes. The less common causes have been noted, and reported recently by Linehan,[1] Grantham-Hill,[2] and Reading.[3] The following case is unusual.

An intelligent young woman, aged 19, in a state of agitation, presented with a history of slight cough, haemoptysis, and a feel-

ing of collapse. She was put to bed, and on examination the following points were noted: temperature normal, pulse rate 120, and regular. Chest: over the third right intercostal space there was an area of surgical emphysema (Dooley's sign positive). In this region there was a profuse concentration of an acneiform eruption, which was present over the chest and back. No evidence of pulmonary disease was found, movement of chest wall, breath sounds, and position of mediastinum being normal. There was minimal tenderness of third right rib. Otherwise no abnormal signs were found. There was a vague history of being "off colour" with diminished appetite, and, in addition, a history of having been struck in the region of the right upper chest the day before. The differential diagnosis at this time was thought to rest between a fracture of the third right rib or possible underlying tuberculosis. She was confined to bed, and the following day the area of emphysema had increased and extended over the right upper chest but not into the neck. No change in her general condition was apparent except that her pulse rate was now 80–90 per minute. During the ensuing week the emphysema disappeared and she was referred for *x*-ray and sputum examination, which were negative.

She reported recurrent haemoptyses during the next three months, and sputum examination was again negative. Eventually she was referred to the local medical specialist, when again examination, including *x*-ray and sputum investigation, was negative. At this time she came to see me again. Having apologized for wasting so much of my time, she volunteered the statement that prior to the swelling of her chest wall she had inserted a hatpin 4 to 6 in. (10 to 15 cm.) long into this area at right angles to the chest wall to a depth of 3 in. (7.5 cm.) (estimated since).

This was an attempt to commit suicide after an unhappy love affair. The patient is now in very good health.—I am, etc.,

Shoeburyness, Essex. M. J. KEHOE.

REFERENCES

[1] *British Medical Journal*, 1950, 2, 762.
[2] Ibid., 1950, 1, 308.
[3] Ibid., 1950, 1, 105.

Neonatal Asphyxia

SIR,—This condition is among the acutest of emergencies that occur in medical practice with only a short reserve of time in which to try resuscitative measures. Your annotation (*Journal*, August 8, p. 328) on the subject reviews well the contemporary methods at our disposal of which but one is simple, safe, and effective and could be carried out by midwife or doctor in the home or in hospital—namely, Akerren's[1] method of resuscitation with "intra-gastric oxygen." Impressed by the idea, this method was given an initial trial and is now regularly used at this hospital on infants with neonatal asphyxia who have failed to respond to the routine procedures of mucus aspiration and tongue traction immediately after delivery. In the past three years it has been used on over 50 occasions with seven failures, and of these only three showed positive necropsy findings. The details of our experience are in the press awaiting publication, and include the description of a light-weight, compact, portable oxygen apparatus about the size of a gramophone-record case which should enable this method to be used both in domiciliary and hospital midwifery practice by midwife or doctor.—I am, etc.,

London, N.W.3. DAVID MORRIS.

REFERENCE

[1] Akerren, Y., and Fürstenberg, N. (1950). *J. Obstet. Gynaec. Brit. Emp.*, 57, 705.

SIR,—Dr. W. N. Leak (*Journal*, August 29, p. 510) has once again recommended the use of analeptic drugs in the treatment of neonatal asphyxia. His arguments are sound, and his practice can be shown to give dramatic results by anyone who takes the trouble to try. Many will, however, object to an intracardiac injection which, in hands other than those of Dr. Leak, may prove to be neither simple nor perfectly safe. The use of the vein in the umbilical cord for this injection is remarkably satisfactory, but a word of warning is necessary. In the state of shock that is typical of "white" asphyxia the umbilical vein will usually be so collapsed as to pass unnoticed unless care is taken to distend a small section by stripping the blood along it. There is a very real tendency to give the injection hurriedly into one of the two obvious vessels, each of which is an artery, and such an injection will not only serve no useful purpose but it may also lead to interference with the circulation in the corresponding buttock or leg.

This is no argument against the use of injections of nikethamide into the umbilical vein, for once the hazard of intra-arterial injection has been appreciated the danger is averted.—I am, etc.,

Birmingham. W. G. MILLS.

Orthopaedics and its Name

SIR,—Regarding the etymology of the word "orthopaedic," I should like to add my bit of knowledge to the different opinions which have been expressed. Here in Greece we use the word "orthopedic" spelt with an e and not ae. It is formed of the words ὀρθός (correct) and the verb παιδάω, which means to fetter, to tie tight, to keep motionless, to correct by means of instruments. The ancient Greeks used the words εὐθειαστική τέχνη, which means the art of straightening, and an orthopaedist was called an εὐθειαστής or a "straightener."

The word "orthopaedic" was introduced by Andry in 1741. He explained the word as "the art of preventing or correcting deformities in children." He may have formed the word from ὀρθός (correct) and παιδεία, which means the art of correct teaching—that is, that which leads man to beauty.—I am, etc.,

Athens. JOHN DOUCAS.

Cancer and the Public

SIR,—Mr. John Gardham (*Journal*, August 8, p. 342) suggests that a comparison of the mortality of doctors and nurses due to cancer, and of the lay public, would go far to prove or disprove the value of cancer education. Such a comparison at first sight is very attractive, and has already been attempted. The difficulty is to obtain sufficient cases in order to compare the same type of case—that is, cancer of the same site—and to compare cases in which symptoms appear at an early stage in the disease, which are the only cases where education can be of any value in saving life.

Dublin and Spiegelman[1] state: "The death rate from cancer among physicians is far below that of the general population. This is probably due to better opportunities for early diagnosis, and for prompt and expert treatment." Total mortality figures, however, contain so many factors that their value in the present argument is doubtful, but the approach made by Robbins *et al.*[2] is on the right lines. After quoting and comparing figures in 1923 and 1948 to show an improvement in early diagnosis among the laity of 57% which they attribute to "educational programmes diverted towards the public," they go on to give figures suggesting that even in "superficial" cancers, which consist of "those cancers that could be detected or suspected by a superficial examination," the percentage of delays in diagnosis is much greater among "doctor patients" than among the public. There are, however, only 53 of these "doctor patients" in the "superficial" group, and no details are given as to the type of superficial cancer among the doctors, nor in the lay patients, with which comparisons are made.

I showed these figures to an English medical statistician, who agrees that there is insufficient detail to prove anything.—I am, etc.,

York. MALCOLM DONALDSON.

REFERENCES

[1] *Postgrad. Med.*, 1947, 2, 188.
[2] *Cancer (N.Y.)*, 1953, 6, 624.

Return to Work

SIR,—In the proceedings of the World Conference on Medical Education (*Journal*, September 5, p. 564) I am wrongly reported as saying that "one of the great factors encountered in occupational health was the unwillingness of many workers to place themselves under medical care owing to their fear of being deprived of their employment." There may be a few who have such fears, but it is nonsense to suggest that it is a factor of any importance.

I did say that there was a tendency for doctors to keep their patients away from work too long, thus delaying their

full recovery, and suggested that the medical student should understand that work has an important therapeutic value in physical and mental rehabilitation.

In my own experience, workers readily seek and accept the advice of industrial medical officers and general practitioners as to their fitness for work.—I am, etc.,

Manchester. RICHARD SCHILLING.

St. Luke's Day Service

SIR,—We should like, through the courtesy of your correspondence columns, to inform your readers of a special service for doctors which is to be held in October for the second year in succession in All Souls Church, Langham Place, W.1 (by Broadcasting House). The date this year is St. Luke's Day itself, Sunday, October 18, and the service will be at 11 a.m. Situated near the centre of the medical world, All Souls, Langham Place, like St. Peter's, Vere Street, which is now united to it, has often been styled "the doctors' church." Many who attended last year's service have encouraged us to arrange another, and we hope that doctors will welcome this opportunity of attending a service of prayer and dedication at the beginning of the academic year.

The President of the Royal College of Physicians and the President of the Royal College of Obstetricians and Gynaecologists have kindly agreed to read the lessons. The preacher will again be the rector.

Seats will be reserved for doctors and members of their family who apply for tickets in advance. Application (stating the number of tickets required) should be made to the church secretary, All Souls Vestry, Langham Place, W.1, by Thursday, October 15.—I am, etc.,

London, W.1. J. R. W. STOTT, Rector, All Souls.

POINTS FROM LETTERS

Selection of Students

Dr. W. A. BELLAMY (Aylesbury) writes: With reference to Dr. Victor Johnson's article (*Journal*, August 29, p. 467), how can any selection committee determine "who are qualified to study medicine and who are not"? The standards of work and outlook, of personality and of temperament, of skill and humour must differ, surely, between the general practitioner and the medical officer of health, between the pathologist and the medical missionary. The article was completely contradicted by Mr. Lionel Norbury's article on the Hunterian era (*Journal*, August 22, p. 405), which states: "Instead of attending school (Hunter) would play truant. . . ." To-day he would have had an adverse report from his headmaster and precious little change from the selection board.

Danger of Penicillin Injection

Dr. J. JAWORSKI (London, W.1) writes: In connexion with the medico-legal article (*Journal*, August 22, p. 446) entitled "Fatal Penicillin Injection," the following case of anaphylaxis is of interest. About a year ago a Polish woman came to my surgery with a swollen, painful knee, recently infected. I injected her with 500,000 units of crystalline penicillin subcutaneously, after which she rested on the couch for a few minutes. When she got up she was extremely pale and did not feel well. I gave her some drops containing tincture of valerian with menthol on sugar to stimulate breathing. She was unable to swallow this, and suddenly she became unconscious. At once I injected ephedrine and nikethamide intramuscularly, but she was no better and I could not feel the pulse. I then injected adrenaline intravenously. After this she showed signs of recovery; I gave her artificial respiration and then breathing was restored. I asked her about previous treatment and was told that she had received penicillin injections about six months previously.

Progress Assessment in Heart Disease

Dr. GEORGE GOMEZ (London, S.W.19) writes: In assessing the progress of patients suffering from heart disease in general practice, a simple method has been found, analogous to the Pulheems classification in the Services, the headings being words ordinarily used by the patients themselves for the most part. The key word is BESCOP, the letters of which stand for breathing, energy, sleep, cough, oedema, and pain (in the chest). The numeral 1 stands for normal or absent (in the case of cough, oedema, and pain); 2 indicates "fair" disability; 3, bad; and 4, very bad.

Obituary

B. SANGSTER SIMMONDS, M.S., F.R.C.S.

The death occurred suddenly on September 3, while he was on holiday in South Africa, of Mr. B. Sangster Simmonds, consulting surgeon to the West London Hospital. He was 66 years of age.

Bernard Sangster Simmonds was born on December 8, 1886, and was educated at Bancroft's School, Woodford Green, and at the Middlesex Hospital, qualifying in 1910. After holding a number of resident posts at the Middlesex Hospital he graduated M.B., B.S. in 1912. He was then in general practice until 1916, when he entered the R.A.M.C. and served in France in the war of 1914–18, attaining the rank of captain. On demobilization he proceeded to the M.S. and obtained the diploma of F.R.C.S. in 1920. His first appointment was as surgeon to a special surgical and neurological hospital of the Ministry of Pensions, but shortly afterwards, in 1921, he was elected to the surgical staff of the West London Hospital, which he actively served for 25 years, for many years in close association with the late Mr. H. Tyrrell-Gray. He was also on the staff of the Hounslow Hospital for over 20 years and, from 1941 to 1951, the Maidenhead Hospital. In addition, he was consulting surgeon to the Infants' Hospital. During the second world war he was surgical adviser to a sector of the Emergency Medical Service. As a surgeon he was calm in manner and scrupulous in technique, and his clinical judgment was greatly valued by his colleagues. His cheerful confidence encouraged his patients, and his inquiring mind and entertaining conversation delighted his friends.

Mr. Sangster Simmonds was president of the West London Medico-Chirurgical Society in 1951–2, and in his presidential address he put forward some interesting ideas—some of them derived from a recent visit to the United States—on hospital and general practice. He took a keen interest in hospital administration, and did useful work for the King Edward's Hospital Fund for London as a member of its council and of several committees. He was always prepared to take time and trouble on projects concerned with the welfare of nurses. A member of the court of the Drapers' Company, he was Master of the Company for two years in succession—a rare distinction—and he took a personal interest in the schools associated with the Company. He leaves a widow, formerly Miss Elsie M. Barwell, whom he married in 1914.

G. R. LEIGHTON, O.B.E., M.D.

Lieutenant-Colonel G. R. Leighton, who died at Ramsey, Isle of Man, on September 8, at the age of 84, was well known in Scotland for his work to improve food hygiene.

Gerald Rowley Leighton was born at Bispham, Lancashire, on December 12, 1868, the son of the late Rev. James Leighton, but he spent part of his youth in New Zealand, where he was a student at Nelson College. Returning to England, he continued his education at the Manchester Grammar School, from which he went on to Edinburgh University to study medicine. He graduated M.B., C.M. in 1895, taking the Scottish triple qualification in the same year, and proceeded to the M.D. six years later. After graduation he was in private

practice in Herefordshire until 1902, when he returned to Edinburgh to devote his whole time to zoology and comparative pathology. In 1903 he was appointed professor of pathology and meat inspection at the Royal Dick Veterinary College, and in the same year was elected a Fellow of the Royal Society of Edinburgh. Ten years later he was invited by the Government to take service with the Local Government Board of Scotland with the express object of establishing a uniform system and standard of meat inspection. His work in this connexion was interrupted by the outbreak of war in 1914, when he was appointed inspector of food contracts for the Admiralty and the War Office, with the rank of lieutenant-colonel in the Royal Army Service Corps. He held the post until 1920, when he was appointed O.B.E. for his services, and for his work as technical adviser to the Ministry of Food from 1915 to 1920.

After the war Colonel Leighton returned to the work which he began in 1913, and, following his report on the subject, the Public Health (Meat Inspection) Regulations came into force in 1924, and Scotland then became the only part of Great Britain to have legal standards of meat inspection. His initiative and his assiduous supervision of the regulations put Scotland ahead of most other countries in the quality and standard of meat inspection. Apart from this work Colonel Leighton served on many Government committees, including the committee on preservatives in foods, and he was instrumental in introducing the system of milk grading in Scotland. He took a prominent part in the investigation of the famous Loch Maree outbreak of botulism in 1922, and his subsequent book on botulism ranked with his book on meat inspection as a standard work. Another important investigation for which he was responsible was on the effect of adding a milk supplement to the diet of Scottish schoolchildren. In 1923 the honorary degree of D.Sc. of the University of Syracuse was conferred upon him. When the British Medical Association held its annual meeting at Edinburgh in 1927 he served as a vice-president of the Section of Preventive Medicine. He retired from the public service in 1933.

Colonel Leighton was a keen naturalist and wrote some well-known books on subjects in which he was particularly interested, including *British Serpents*, *British Lizards*, *Embryology*, and *The Life and Work of Huxley*. He also founded the *Field Naturalists' Quarterly* in 1902, and in 1909 he edited the *Modern Veterinary Adviser*. He is survived by a widow and one daughter.

NORMAN C. KING, T.D.

Colonel Norman C. King, a former Registrar of the General Medical Council and of the Dental Board of the United Kingdom, died on August 21, at the age of 82.

Born on February 19, 1871, Norman Carew King was educated at Haileybury College. In 1897 he entered the service of the General Medical Council, and ten years later was appointed assistant secretary. He had therefore had considerable experience of the Council's business before he was appointed Registrar in 1911, shortly after Sir Donald MacAlister entered upon his long period as President of the Council. King's knowledge of the Council's work and his innate organizing ability enabled him to improve in many ways the office administration and to increase its efficiency by the introduction of more modern methods of dealing with the steadily growing *Medical Register*.

An enthusiastic Territorial officer, King joined the London Rifle Brigade in 1892, and soon after the outbreak of war in 1914 went to France in command of a company of his regiment. He served with distinction, being mentioned in dispatches, and attained the rank of brevet colonel. After the war he resumed his duties as Registrar of the General Medical Council, and when the duty of maintaining the *Dentists Register* was transferred in 1921 to the newly formed Dental Board of the United Kingdom he was given the additional appointment of Registrar of the Board.

Those who served under him in war and in peace recognized with respect and affection his ability as a leader, his energy and enthusiasm, and his capacity for encouraging others, by a judicious delegation of duties, to develop their own abilities and accept further responsibilities. When he retired in 1933 from his dual position as Registrar of the General Medical Council and of the Dental Board tributes were paid to him by both bodies, including a special reference by the Chairman of the Board, Sir Francis Acland, to his success in the difficult task of serving two masters.

In the last twenty years of his life King continued to take an active interest in Haileybury College, serving on the Council and editing the College *Register* in 1946, and in the London Rifle Brigade. He underwent several major operations, including the amputation of a leg, but, facing his ordeals with a remarkable courage and absence of self-pity, he remained active until within a year of his death.

Dr. G. P. ANNING, who was well known as a general practitioner in Leeds for over 50 years, died at Ripon, Yorkshire, on August 30 at the age of 80. George Paul Anning studied medicine at Leeds, gaining prizes at the Yorkshire College in theoretical and practical chemistry and in materia medica. After qualifying in 1897 he held the appointment of senior house-physician at the General Infirmary at Leeds, and was for a time prosector in anatomy at the Yorkshire College. After settling in practice in the Kirkstall area, he became honorary medical officer to the ophthalmic department of the Leeds Public Dispensary, and for some years was visiting surgeon to the Ministry of Pensions Special Surgical Hospital. A member of the North of England Obstetrical and Gynaecological Society, and of the Leeds and West Riding Medico-Chirurgical Society, he was a member of the council of the former society for some years. A keen Territorial, he attained the rank of captain in the R.A.M.C., and during the war of 1914–18 he served on the staff of the Beckett Hospital, Barnsley. He retired in 1951 on account of ill-health, and went to live with his son, Dr. R. M. H. Anning, at Ripon. Dr. Anning's wife died not long ago, and he is survived by his younger son and a daughter, his elder son having been killed in 1931 while serving with the Royal Air Force. His brother, Dr. J. J. Anning, is in practice at Leeds, and his nephew, Dr. S. T. Anning, is a specialist in dermatology, also at Leeds.

We are indebted to Professor C. W. VINING for the following appreciation : By the death of Dr. G. P. Anning the Leeds medical profession has lost an outstanding and greatly respected general practitioner. "G. P.," as he was always known to his many friends, was a great character, with an interesting and distinctive personality. His monocle, which was worn to correct a unilateral eye defect, gave him a notable and an aristocratic appearance, which his dapper figure accentuated. His way of looking one straight in the face when talking was very characteristic, and is one reason why our memory of him will

remain vivid. He was a very courteous man, with great charm of manner, and the type of man one would choose to discuss some subject where confidence was essential. He had a strong sense of humour, which he would display in dealing with the foibles and questionable behaviour of others. He hated humbug, hypocrisy, and window dressing, and was quick to recognize them. He was, indeed, a fine judge of character and of that which was genuine in men and things, and he steered his way through life by means of honesty of purpose and sound common sense. In other words, he was the kind of practitioner one would choose to look after one's family and oneself : one instinctively knew that "G. P." would stand foursquare against unpleasant investigations and treatment unlikely to be beneficial. He was always interested in young people and watched their development with real sympathy, and few could surpass him in his ability to handle small children. No doubt they appreciated his humour, which was always unfailing.

Anning was closely associated with Moynihan and Mayo Robson. He always wished to be a surgeon, but was prevented from sitting for his Fellowship owing to illness. Nevertheless he was a general-practitioner surgeon in his early days, and during the first world war he did major surgical work at the 2nd Northern General Hospital at Leeds. He assisted Moynihan at what was probably his earliest operation for duodenal ulcer, a case which Anning himself had diagnosed in his own practice and which was referred to in Moynihan's earliest book on surgery. In 1900 he reported in the *Transactions of the Obstetrical Society of London* a case of primary ovarian pregnancy, which is believed to be the first reference to this unusual condition to be published. The specimen was in the museum of the Royal College of Surgeons of England, but was destroyed by enemy action during the second world war. To the end of his days Anning remained interested in all that was going on, and no one could ever have dubbed him out of date. He enjoyed life to the full, but in doing so his profession always came first. Always cheerful himself, he enjoyed the company of others and believed that the great thing to strive for was happiness and friendship. He found his chief relaxation at his beloved Alwoodley, where he enjoyed golf up to quite recent years, and where he found great joy in his many friends until the end. He was a connoisseur of beautiful things and was never so happy as when showing his collection—glass was his special weakness—when entertaining his numerous friends. His memory will remain as a colleague who displayed outstanding qualities during his whole life.

Dr. DENIS JOHN DALTON died in the London Hospital on August 18, at the age of 27. Born on January 17, 1926, he attended the Catholic School of Annunciation, from which he obtained a scholarship to the Cardinal Vaughan School, being transferred subsequently to University College School, Hampstead, where he passed the first M.B. examination. He then entered the London Hospital Medical School and graduated M.B., B.S. in 1949. His hypothesis entitled "The Eosinophil Leucocyte, Eosinophilia, and Allergy" was published in the *Lancet* while he was still a student. After six months as a house-physician at the London Hospital, and eighteen months at the King Edward Memorial Hospital, Ealing, he was awarded a grant by the Dan Mason Research Foundation, for whom he prepared a report on "The importance of certain lipoids and their components as protease-inhibitors." He developed a keen interest in allergy and diseases of the blood, but, preferring the work of a hospital with its personal contacts to the somewhat secluded life of a research worker, he obtained an appointment as medical registrar at the City Hospital, Derby. In February last he returned to the London Hospital as a patient, and a malignant tumour was removed from his spine. After a period of convalescence and a brief return to his duties, he was again admitted to the hospital with acute leukaemia, from which he died. The many tributes from colleagues and friends emphasized his capacity for friendship, the promise of a brilliant career, and his devotion to the Catholic faith.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 29** (No. 34) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	16	0	7	0		23	5	6	1	2
Dysentery	206	35	76	1	2	119	26	81	1	1
Encephalitis, acute	2	1	0	2		3	0	1	0	1
Enteric fever:										
Typhoid	1	0	0	1		13	0	0	0	1
Paratyphoid	16	0	0	0		58	0	2 (B)	2	
Food-poisoning	194	15		4		190	16		1	
Infective enteritis or diarrhoea under 2 years				16	47				20	39
Measles*	1,049	20	36	27	22	5,256	573	25	22	61
Meningococcal infection	29	5	11	1		29	3	13	1	
Ophthalmia neonatorum	20	5	2	1		39	4	8	0	2
Pneumonia†	193	8	104	4		207	13	115	4	1
Poliomyelitis, acute:										
Paralytic	120	9	10	23	7	152	12	11	9	3
Non-paralytic	117	5				68	4			
Puerperal fever§	219	27	14	1		244	33	10	1	
Scarlet fever	443	23	115	21	29	559	43	139	12	30
Tuberculosis:										
Respiratory			127	32				137	29	
Non-respiratory			22	4				30	5	
Whooping-cough	4,170	402	457	29	42	1,800	75	123	46	112

DEATHS in Great Towns	1953					1952				
	Eng. & Wales	Lond	Scot.	N. Ire	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0		0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years	12	2	1	0	1	2	0	0	1	4
Influenza	1	0	0	0	0	5	1		0	0
Measles		0	0	0			0	1	0	0
Meningococcal infection		0	2				1			
Pneumonia	112	16	13	8	2	99	9		6	6
Poliomyelitis, acute	5	2			0	8	2			0
Scarlet fever		0	0	0	0		0		0	0
Tuberculosis:										
Respiratory	60	10	6	3	3	83	9	12	3	8
Non-respiratory		3	4	0	1		3	1	2	0
Whooping-cough	4	0	1	2	0	1	0		0	0
Deaths 0–1 year	217	22	25	8	18	189	25	31	8	19
Deaths (excluding stillbirths)	4,075	562	502	98	137	3,953	585	486	94	139
LIVE BIRTHS	7,461	1117	855	218	329	7,194	1074	807	207	417
STILLBIRTHS	180	15	22			170	23	32		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

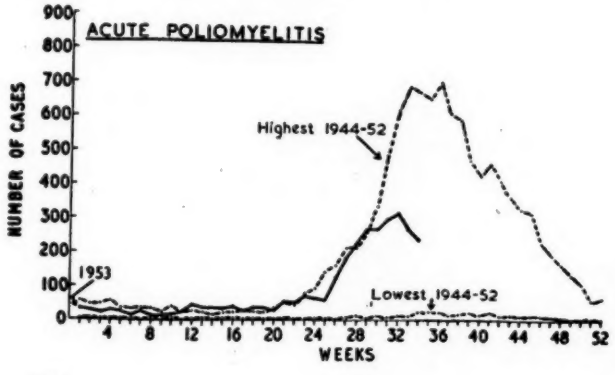
Poliomyelitis

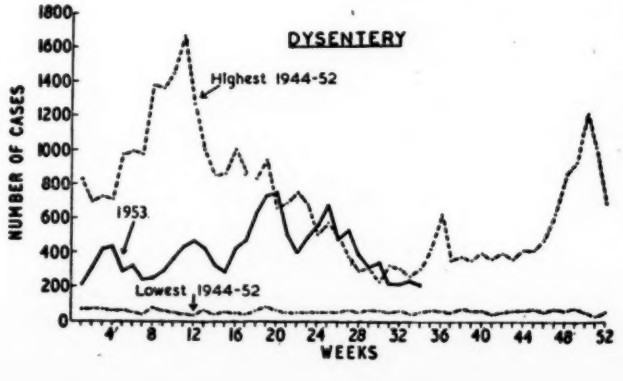
Poliomyelitis notifications (uncorrected) in the week ended September 5 (thirty-fifth week of the year) were as follows : paralytic, 123 (120); non-paralytic, 101 (117); total, 224 (237). This is a decrease of 13 compared with the previous week, the figures for which are in parenthesis. The individual districts which have notified 20 or more cases in the year to September 5 (with incidences per 100,000 in parenthesis) are as follows : Southend-on-Sea C.B., 47 (31.02); Liverpool C.B., 56 (7.08); Birmingham C.B., 68 (6.08); Coventry C.B., 124 (47.51); Leicester C.B., 30 (10.49); Lewisham Met. Boro., 26 (11.45); Blackpool C.B., 32 (21.72); Camberwell Met. Boro., 22 (12.14); Islington Met. Boro., 26 (11.05); Bournemouth C.B., 40 (28.00); Bristol C.B., 28 (6.31); Nottingham C.B., 25 (8.05); Taunton M.B., 28 (80.92); St. Pancras Met. Boro., 23 (16.48); Carlisle C.B., 26 (38.29); Manchester C.B., 23 (3.26); Wandsworth Met. Boro., 21 (6.33); Southampton C.B., 21 (11.97); Atherstone R.D., 21 (88.61); Leeds C.B., 22 (4.36); Cambridge M.B., 20 (22.04); West Ham C.B., 20 (11.73); Kingston-upon-Hull C.B., 22 (7.35).

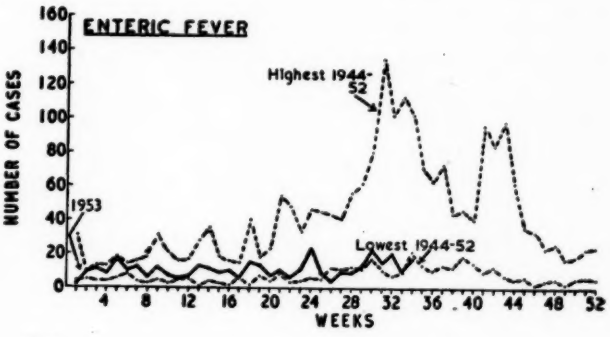
Although there was a small decrease in the total notifications for the week compared with the preceding week, there was an increase of 3 in the number of paralytic cases. These figures represent a check in the marked fall in notifications of the preceding two weeks. The disease is nevertheless widely distributed, and there is no indication of the development of an epidemic. We may continue to be cautiously optimistic.

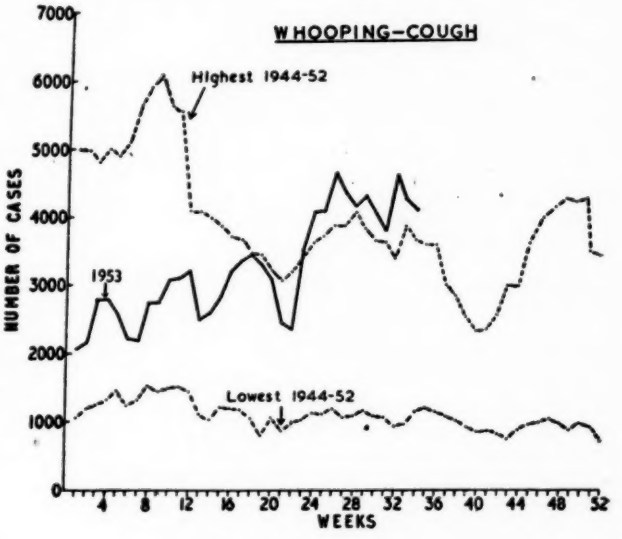
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The only fluctuations of any size in the notifications of infectious diseases in England and Wales during the week ending August 29 were decreases of 509 for measles, from 1,558 to 1,049, and 171 for whooping-cough, from 4,341 to 4,170.

The largest declines in the notifications of measles were 66 in Lancashire, from 215 to 149, and 56 in Yorkshire West Riding, from 159 to 103. Only small fluctuations occurred in the trends of whooping-cough, with the exception of a fall of 101 in Essex, from 410 to 309. 443 cases of scarlet fever were notified during the week—12 more than in the preceding week—and no large variations in trend were recorded. The number of notifications of diphtheria rose from 11 to 16; the chief feature of the returns was an increase from 0 to 3 in Durham.

237 cases of acute poliomyelitis were notified during the week, and these were 24 fewer for paralytic and 9 fewer for non-paralytic cases than in the preceding week. The largest returns were Lancashire 19 (Blackpool C.B. 5), Warwickshire 17 (Birmingham C.B. 6, Coventry C.B. 6), Essex 15 (Southend-on-Sea C.B. 3), London 14, Yorkshire West Riding 12, Yorkshire East Riding 11 (Beverley R.D. 8), Dorsetshire 11 (Weymouth and Melcombe Regis M.B. 3), Southampton County 11 (Bournemouth C.B. 5), Somersetshire 11 (Yeovil R.D. 4), Surrey 10 (Woking U.D. 3), and Middlesex 10.

206 cases of dysentery were notified during the week, and these were 29 fewer than in the preceding week. The largest centres of infection were London, with 35 cases scattered through 12 boroughs; Cornwall, 28 (Truro R.D. 27); Yorkshire West Riding, 23 (Bradford C.B. 7); Lancashire, 22; and Middlesex, 13.

Week Ending September 5

The notifications of infectious diseases in England and Wales during the week included scarlet fever 483, whooping-cough 4,058, diphtheria 20, measles 802, dysentery 205, paratyphoid fever 11, typhoid fever 9, and food-poisoning 256.

Medical News

Modern Philanthropy.—The latest annual report of the Nuffield Foundation underlines once again the discrimination and discernment with which the Foundation's great resources are applied. The declared objects of the Foundation are the advancement of health and the prevention and relief of sickness, the advancement of social well-being, the care and comfort of the aged poor, and the advancement of education. These ends are served not only by the support, on occasion, of large projects, but mostly by the patient seeking out of the small but promising experimental venture at a stage when private support may make all the difference between success and failure. The Foundation's preference is for the small initial grant. During the financial year 1952–3 £713,696 was disbursed in grants for research in the United Kingdom and Commonwealth. About £320,000 was for work in Britain, the amount being divided between biological, "other scientific," and social research in the proportion of 3:2:1. Grants of special medical interest include: £5,000 to the Royal Cancer Hospital, where television techniques, ultrasonics, and the combination of radioactive isotopes with conventional radiography are being developed as aids to diagnosis; £15,000 (over five years) to the Lister Institute for the study of non-specific defence mechanisms of the body in the early stages of infection; £10,200 to the Department of Anatomy, University College, London, for further work on the electronic "flying-spot" microscope, an instrument designed to magnify, measure, and count particles automatically; and further support for Professor P. B. Medawar's work on the immunity reactions which interfere with grafting operations. Medical fellowships were awarded to three United Kingdom and 10 Dominion doctors; all the latter came to study in Britain. The Foundation has promised the National Corporation for the Care of Old People a further £250,000 to assist with pioneering schemes for the welfare of old people.

Physiotherapists in Congress.—Last week in London the World Confederation for Physical Therapy, under its president Miss Mildred Elson (U.S.A.), completed a most successful First Congress. The Confederation is a league of recognized physical therapy organizations which was formed as a result of a conference called in 1948 by the Chartered Society of Physiotherapy. After an official opening on September 7 by the Minister of Health the Congress got down to a full programme of lectures, discussions, demonstrations, visits, and receptions. Medical speakers addressed the Congress on physical therapy in neuromuscular disorders, in the rheumatic diseases, and in chest diseases. There was a symposium on physical therapy in industry, and visits were made to many hospital departments and rehabilitation centres. The social functions included receptions at B.M.A. House, the Guildhall, and the Apothecaries' Hall, and a dinner and dance at the Park Lane Hotel. The Chartered Society of Physiotherapy was the host organization of the Congress, and Professor J. Whillis, chairman of council of the Chartered Society, was the Congress chairman.

Wellcome Research Laboratories.—Dr. J. W. Trevan, F.R.S., has retired from his position as research director of the Wellcome Foundation Ltd., and director of the Wellcome Research Laboratories, Beckenham, after 33 years' service with the company. His place is taken by Mr. D. W. Adamson, D.Phil., formerly head of the chemical division of the Wellcome Research Laboratories.

Professor Arnold Sorsby, research professor in ophthalmology at the Royal College of Surgeons and Royal Eye Hospital, has been elected secretary-general of the International Organization Against Trachoma. This body was founded in 1929 by the Thirteenth International Congress of Ophthalmology.

COMING EVENTS

Royal Statistical Society.—The study circle on medical statistics will meet at 6.45 p.m. on September 29 in the Westminster Medical School, S.W.1, and Dr. V. H. Springett, of the Ministry of Health Mass Radiography Unit, will read a paper on the follow-up problems arising from his work.

Institute of Dermatology.—The winter course of lectures, for which no charge is being made this year, begins on October 2. The syllabus includes subjects allied to dermatology. Systematic lectures will be given on Tuesdays and clinical demonstrations on Fridays: lectures are, wherever possible, complementary to demonstrations. Lectures and demonstrations on pathology, including medical mycology, will continue to be given on Wednesdays and Thursdays, and lectures on *x*-ray techniques will be included on some Wednesdays.

London School of Hygiene and Tropical Medicine Association.—A dinner of the School Association will be held at Frascati's Restaurant in London on Friday, October 16. There will be dancing afterwards, and each member may bring one guest. Tickets (25s. each) may be obtained from Miss K. M. Shaw, London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Thursday, September 24

LONDON HOSPITAL.—In Bearsted Theatre, 4.15 p.m., Dr. Stephen Rothman (Chicago): Some Aspects of the Physiology of the Skin.

Friday, September 25

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—7.30 p.m., Dr. R. L. Kahn (U.S.A.): Clarifying Syphilitic and Non-syphilitic Sero-diagnostic Reactions.

● ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS.—5 p.m., William Blair-Bell Memorial Lecture by Mr. James Walker: Foetal Anoxia—A Clinical and Laboratory Study.

APPOINTMENTS

CAIRNS, ROBERT OLIVER, M.B., Ch.B., D.P.H., Medical Superintendent, Glasgow Children's Group of Hospitals and New Hospital at Alexandria, Vale of Leven.

HARRISON, G. J., L.R.C.P.&S.I., D.P.M., Medical Superintendent, Winwick Hospital, Winwick, Warrington.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bell.—On August 31, 1953, at Cambridge to June Drusilla (formerly Cross), M.B., B.S., wife of David James Bell, Sc.D., a daughter.

Frankenberg.—On September 1, 1953, at the Weir Maternity Hospital, London, to Mieke (formerly Van Tricht), wife of John Frankenberg, M.R.C.O.G., a third daughter—Anne Marijke Julia.

Halle.—On August 25, 1953, at Sheffield, Yorks, to Frances (formerly Saunders), M.R.C.S., L.R.C.P., wife of Hugh Halle, M.R.C.S., L.R.C.P., a daughter.

Kennedy.—On September 9, 1953, at Johnstone House, Belfast, to Bridget, wife of Terence Kennedy, M.S., F.R.C.S., a daughter.

MARRIAGES

Duncan—Spence.—On September 4, 1953, at the High Kirk, Rothesay, Bute, John Duncan, L.R.C.P.&S.Ed., L.R.F.P.S., of Carntyne, Glasgow, to Myra Reid Spence, of Rothesay, Bute.

DEATHS

Button.—On August 19, 1953, at "Rotherview," Rye, Sussex, Martin Binns Studer Button, F.R.C.S.

Cobb.—On August 15, 1953, at Broome Lodge, Norfolk, Ivo Geikie Cobb, M.D., of 30, Harley House, London, N.W., aged 66.

Harper.—On August 12, 1953, in Victoria, British Columbia, Canada, John Harper, M.R.C.S., L.R.C.P., L.D.S., formerly of London, W., and Rottingdean, Sussex, aged 87.

MacLachlan.—On August 26, 1953, at 11, Barrington Drive, Glasgow, C., Lewis MacLachlan, M.B., C.M., D.P.H., formerly of 14, Ruskin Terrace, Glasgow, W.

O'Driscoll.—On August 19, 1953, Patrick Lawrence O'Driscoll, M.B., B.Ch., of Courtmacsherry, Co. Cork, formerly of Timoleague, Co. Cork, aged 76.

Purdy.—On August 28, 1953, at his home, 91, Percy Avenue, Kingsgate, Broadstairs, Kent, Wilfrid John Purdy, M.B., Ch.B., F.R.M.S., aged 71.

Rotenstein.—On August 13, 1953, at Brighton, Sussex, Hynek Ignac Rotenstein, M.D., of 22, Palace Court, London, W., aged 58.

Rowden.—On August 16, 1953, in a nursing-home, Harrogate, Leonard Alfred Rowden, D.Sc., M.B., C.M., F.F.R., of 3, Oakwood Lane, Roundhay, Leeds, Yorks, aged 82.

Watt.—On August 14, 1953, at 935, Foulbay Road, Victoria, British Columbia, Canada, Walter Langmuir Watt, C.M.G., V.D., M.D., Colonel, C.A.M.C., retired, late of 5, Queen Anne Street, London, W., and Sussex, aged 77.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Meconium and Foetal Distress

Q.—*Textbooks repeatedly warn us that meconium-stained liquor, especially when associated with irregularity of the foetal heart, indicates some foetal distress. What is the significance of the passage of meconium-stained liquor when not associated with irregularity of the foetal heart rate? What should one's action be when this occurs before the start of labour—for example, after premature rupture of the membranes—and during labour?*

A.—It is assumed that this question applies to a vertex presentation of the foetus.

The passage of meconium without any change in the rate or rhythm of the foetal heart is relatively common. It is more often seen when the pregnancy has gone beyond the date of expected delivery as calculated from the last menstrual period, and also if the mother has been given quinine. It may also be a sign of foetal malformation. Nevertheless there is often no obvious cause or associated factor. The occurrence is not necessarily of serious significance, but it is never possible to view it without some anxiety and to wonder if it is a forerunner of more definite signs of foetal distress. This is especially true if there is passage of thick meconium rather than slight staining of liquor.

If meconium is passed during labour a careful examination, including radiography if possible, should be made to exclude breech presentation or any other sort of abnormality. If none is found, the usual procedure is to allow labour to progress whilst paying extra attention to the foetal heart, being ready to intervene in the interests of the child at the first sign of any change in its rate and rhythm. It is difficult, however, to lay down hard and fast rules, and each case has to be judged on its merits. Factors such as the age and fertility of the expectant mother, and the speed with which the cervix is dilating, might well determine interference. If there is evidence of post-maturity most obstetricians tend to take a rather more serious view of the passage of meconium, particularly if the meconium is first seen when the membranes are artificially ruptured to induce labour. Indeed, if puncture of the membranes in a case of post-maturity reveals meconium and very little liquor, and if labour does not commence soon and progress rapidly, caesarean section may well be indicated in the interests of the foetus.

Ouabaine in Cor Pulmonale

Q.—*Has ouabaine any advantages over digitalis in the treatment of cor pulmonale?*

A.—There is no convincing evidence that ouabaine or any other strophanthin preparation has any advantage over digitalis in the treatment of cor pulmonale. The confusion surrounding this question is largely due to the hypothesis put forward a few years ago that digitalis improved the circulation in heart failure by lowering the venous pressure directly[1]; it was believed that such an action was undesirable in cor pulmonale because the raised venous pressure in that condition seemed to be nicely adjusted to help maintain a maximum cardiac output; if it were lowered directly by venesection, for example, the output fell.[2]

It should be understood that a raised cardiac output is beneficial in cor pulmonale, for it helps to compensate for the anoxia. In reinvestigating the action of digitalis-like drugs on the cardiac output and venous pressure, McMichael switched to studying strophanthin, and showed that ouabaine increased the cardiac output in heart failure without necessarily lowering the venous pressure.[3] It followed that ouabaine, at any rate, would be expected to benefit cases of cor pulmonale showing clinical signs of heart failure. There is a good deal of evidence, however, that digitalis does not act as a primary venous-pressure-lowering agent, but as a direct cardiac tonic in all cases of heart failure, and there is no contraindication to its use in cor pulmonale. There is no real evidence that ouabaine or any other strophanthin preparation has any advantage over digitalis in this respect.

REFERENCES

1 McMichael, J., and Sharpey-Schafer, E. P. (1944). *Quart. J. Med.*, **13**, 123.
2 Howarth, S., *et al.* (1947). *Clin. Sci.*, **6**, 187.
3 McMichael, J. (1948). *British Medical Journal*, **2**, 927.

Salt in the Water Supply

Q.—*In this district some wells have been flooded with sea water, and it is likely to be some time before they revert to normal. What is the highest saline concentration compatible with their use for drinking? Are there any risks to health from the continued use of a saline water supply, assuming it to be pure in other respects? While it might seem that taste would serve as a rough guide, it has been found that some householders complain of the taste, while others, where the estimated salinity of the supply has been found to be double, notice nothing abnormal.*

A.—The question of the upper limit of salinity of a water compatible with its use for drinking is not one which can be answered exactly. The threshold concentration of sodium chloride—the principal mineral constituent of sea water—perceptible by taste varies considerably from one person to another. Some people can taste salt in a concentration of 300 parts per million, while others cannot detect it below, say, 700 parts per million. Some underground waters, principally in Essex, contain appreciably more even than this and have been consumed regularly by people accustomed to them. Broadly, however, it may be said that for consumers unused to saline water an upper limit of 500 parts per million of sodium chloride would be generally acceptable. Assuming, as in the question, that the water is pure in other respects, there would be no risk to health, for not only would the daily consumption of salt be insignificant, but the other mineral constituents of sea water would be present in much lower concentrations. Magnesium sulphate, for instance, is present in sea water to the extent of rather less than one-tenth of the sodium chloride, and the daily intake from the water supply would therefore not approach a medicinal dose.

Swelling of Eyelids after Thyroidectomy

Q.—*Following a subtotal thyroidectomy performed about 15 months ago, a female patient of mine experiences gross swelling of both eyelids (especially the upper) as a result of any form of excitement. This swelling causes epiphora and blurring of vision. Her thyrotoxic symptom disappeared soon after operation. What is the possible aetiology of this condition, and what treatment would you advise in her case?*

A.—Swelling of the eyelids after thyroidectomy may be due to post-operative hypothyroidism. This can usually be diagnosed clinically by increasing weight, thickening and coarsening of the skin, a tendency to water retention, deficient perspiration, and sensitiveness to cold. Occasionally the diagnosis is not obvious, and it may be worth while testing for hypothyroidism by measuring the basal metabolic rate or by the use of one of the various radioactive iodine tests. The symptom may also be a precursor of post-operative exophthalmos. In such instances it is usually possible by palpation to detect a bulging of the orbital contents behind the upper lids. There is often an associated injection of the conjunctiva. Later on a measurable exophthalmos or diplopia may develop. In neither case, however, would one expect the symptom to be affected by any form of excitement, and the question arises whether this symptom

has in fact any relationship to the preceding thyroidectomy. Some form of allergic reaction might conceivably be involved.

The treatment for post-operative hypothyroidism is the administration of thyroid extract. There is no known treatment for post-operative exophthalmos.

Severe Knock-knee in a Child

Q.—*What treatment is advised for a boy of 5½ years with severe knock-knee which has not responded to wedging of the shoes?*

A.—The question is a little difficult to answer, as the amount of knock-knee is not specified. However, at 5½ years one would not consider osteotomy if the deformity was less than 4 inches (10 cm.) between the internal malleoli with the knees straight, and even this amount is not an absolute indication for operation. Sometimes even at this age the knock-knee may spontaneously decrease in amount, though it can be taken as definite that it will not disappear altogether without treatment. However, no conservative treatment is likely to be useful now that the bones are relatively mature.

In many ways the simplest method of treating a knock-knee is by stapling the inner side of the lower femoral epiphyses. Although it has been done at this age, there are theoretical risks that the epiphyses may be permanently arrested; it is therefore the consensus of opinion that stapling should be delayed until the age of 8.

D.D.T. and Dermatitis

Q.—*Is dermatitis recognized as a reaction to a D.D.T.-containing insecticide? Exposure consisted only in living in a house which had been sprayed with the insecticide and not in handling the liquid. Dermatitis has followed such exposure on three separate occasions. Is it possible to desensitize the patient?*

A.—Allergic eczematous dermatitis from D.D.T. is by no means unknown. In the case described the sensitivity appears to be of a very high order, and it would be as well to confirm the existence of sensitivity with patch tests to D.D.T. before the diagnosis is considered established. It is not clear whether, in the case described, other possibilities have been excluded. Attempts at desensitization might well produce extremely severe reactions and, even so, are not likely to be successful. If a sensitivity such as this is once established it is essential for the patient completely to avoid all contact with the substance in the future.

Polaroid Spectacles and the Spread of Infections

Q.—*Is there any danger of infection of the skin in wearing the polaroid spectacles provided for viewing three-dimensional films?*

A.—It seems unlikely that any infection would be conveyed from one person to another in this way. If the spectacles came into actual contact with a lesion of impetigo contagiosa or with furuncles discharging staphylococcal pus the infection might be conveyed to another person. Similarly ringworm infection might be transmitted, particularly among children. Although the risks of spreading infection in this way are not at present great, it would seem advisable for cinema managements to bear this matter in mind.

Cyanide Poisoning and Nitrates

Q.—*Is amyl nitrate (as distinct from amyl nitrite) used in the treatment of cyanide poisoning? If so, is it effective?*

A.—Nitrites are used in cyanide poisoning in order to bring about the conversion of some of the haemoglobin to methaemoglobin. This in turn reacts with the cyanide. Nitrates do not react with haemoglobin. Some methaemoglobin may be formed after the administration of nitrate, but this is probably due to the conversion of some nitrate to nitrite. As speed is essential to success in the treatment of cyanide poisoning the administration of nitrate would be of no value.

NOTES AND COMMENTS

Treatment of Fibrositis.—Mr. CLIFFORD S. JAMES (Auckland, New Zealand) writes: In "Any Questions?" (June 20, p. 1403) your writer on fibrositis recommends 1% procaine for injection and suggests limiting the dose to 10 ml. to avoid toxic and sensitivity reactions. Since seeing an account of the treatment of football injuries on the field by the injection of local anaesthetic into the injured part, I conceived the idea of treating fibrositis by this method, using the same local anaesthetic that I used for my operations—namely, cinchocaine hydrochloride 1/2,000. Over this period (more than 10 years) there have been times when the giving of these has been almost a daily event, and I have had no signs of any toxicity or sensitivity, and, provided that my technique has been correct, and the injection has been given exactly into the centre of the tender spot, my results have been very satisfactory. The proof that the injection is correctly placed is (*a*) that it is somewhat painful when given, whereas if wrongly placed it is not; and (*b*) that the patient should be able within a short time of the injection to carry out painlessly the movements that had been painful before. When seen seven and fourteen days later, the patient reports that the original pain disappeared completely following the injection. Some say there was a slight soreness afterwards, but this cleared in 48 hours. If this report is not forthcoming, it means (*a*) that the spot, which may be no more than a thin thread of tissue, has been missed, or (*b*) that too little fluid has been injected where the lesion has been large, or deep and indefinite, and fluid has been wasted in the superficial tissue, or (*c*) that there have been two or more spots, but only one has been detected and injected. This is usually the more painful one, and the lesser one shows up later. In any of these cases a further injection has to be given, but with experience this becomes an infrequent occurrence.

I have worked on the theory that, while the local anaesthetic dulls the pain, the fluid diffusing through the lesion opens it up for the blood to clear it away. The amount of fluid injected varies with the size and depth of the focus from 2 ml. to 20 or even 30 ml., and, with more than one spot to be done, up to 50 or 60 ml. may be used at one sitting. The 10 ml. of procaine would often be insufficient, whereas on the other hand the maximum of cinchocaine hydrochloride 1/2,000 allowable[1] is 30 ml. per stone (6.4 kg.)—that is, 300 ml. for a man of 10 stone (64 kg.) body weight. This great margin of safety is so large that, in the treatment of fibrositis, toxicity need hardly be considered. This has been my experience. I have met no signs of toxicity in these 10 years. On these grounds cincochaine hydrochloride 1/2,000 would appear to be preferable to procaine 1% with its risk of toxicity and sensitivity. The solution for injection, made up in the following order, is: cinchocaine hydrochloride, gr. ¼ (50 mg.); sterile water, 3½ oz. (100 ml.); dilute acetic acid, 1 drop.

REFERENCE

[1] Organe, G., *Lancet*, 1942, 2, 33.

OUR EXPERT writes: I agree entirely with the various points raised by Mr. James on the treatment of fibrositis with injections of local anaesthetic, and that cinchocaine hydrochloride is a satisfactory alternative to procaine. I do not think it matters greatly what anaesthetic agent is used, but what does matter is that the solution should be freshly made up before use and free from adrenaline or preservative agent.

Correction.—The reference to Robert Klaber's work on phytophoto dermatitis ("Any Questions?" August 22, p. 449) should have been: *Brit. J. Derm.*, 1942, 54, 193.

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